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Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

04290467.2

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Demande no:

Anmeldetag:
Date of filing: 20.02.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

AstraZeneca AB

151 85 Södertälje
SUEDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

In Anspruch genommene Prioriät(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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CHEMICAL COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

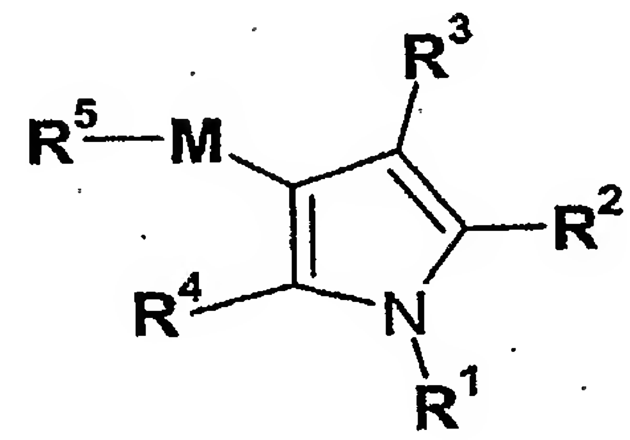
Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/55119 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists: WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),



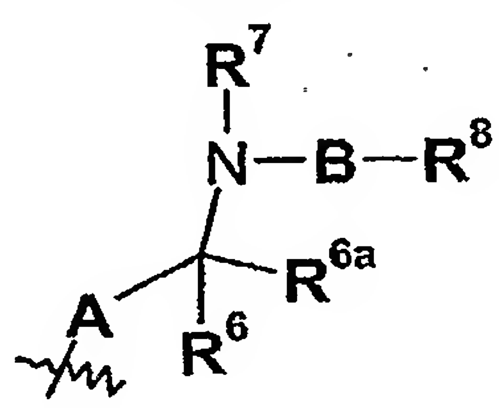
Formula (I)

wherein:

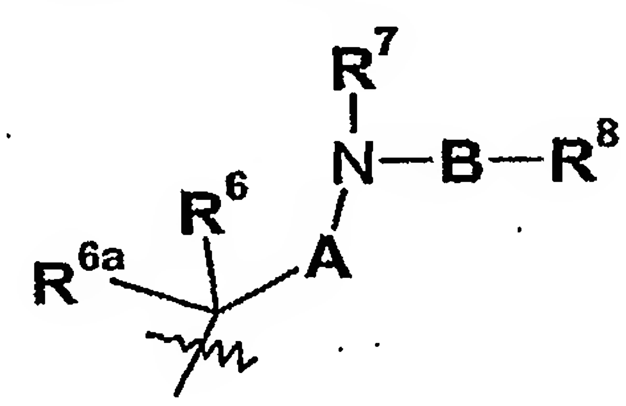
$\mathbf{R^1}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl or optionally substituted arylC_{1-6}alkyl, wherein the optional substituents are selected from C_{1-4}alkyl, nitro, cyano, fluoro and C_{1-4}alkoxy;

$\mathbf{R^2}$ is an optionally substituted mono or bi-cyclic aromatic ring, wherein the optional substituents are 1, 2 or 3 subsituents independently selected from: cyano, $\mathbf{R^e}\mathbf{R^f}$N-, C_{1-6}alkyl, C_{1-6}alkoxy, halo, haloC_{1-6}alkyl or haloC_{1-6}alkoxy wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are independently selected from hydrogen, C_{1-6}alkyl or aryl;

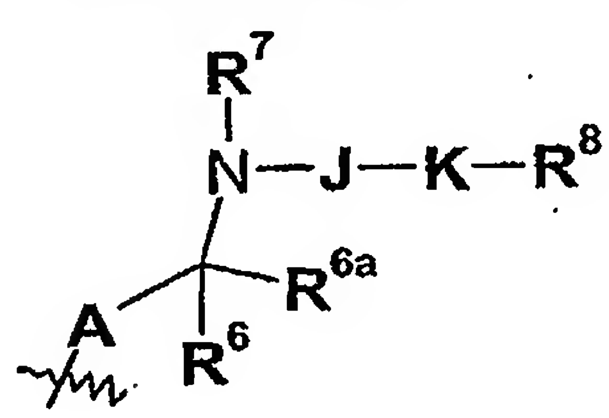
$\mathbf{R^3}$ is selected from a group of Formula (IIa) to Formula (IId):



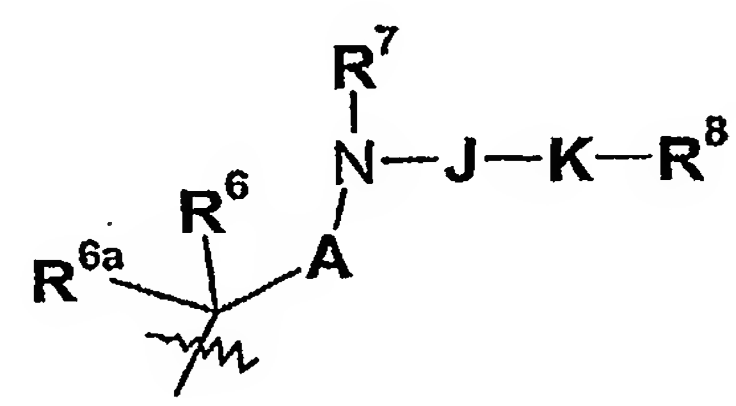
Formula (IIa)



Formula (IIb)



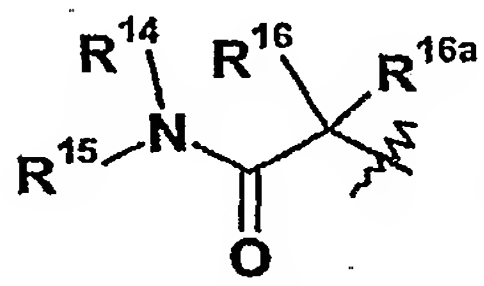
Formula (IIc)



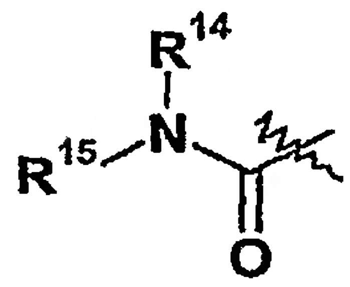
Formula (IId)

R^4 is selected from hydrogen, $C_{1\text{-}4}$alkyl or halo;

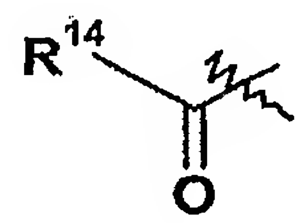
R^5 is selected from a group of Formula **III-a; III-b; III-c; III-d; III-e; III-f, III-g , III-h, III-i,** or **III-j, III-k, III-l, III-m, III-n** or **III-o**



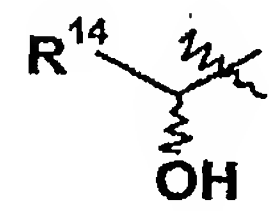
III-a



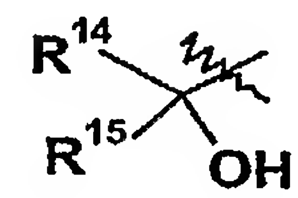
III-b



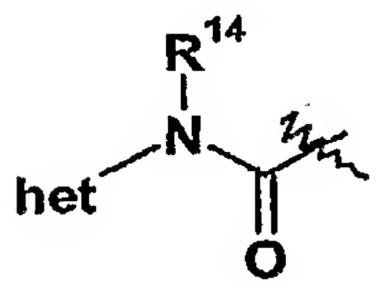
III-c



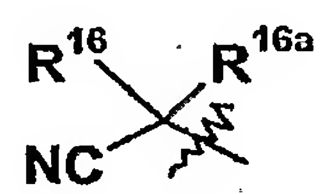
III-d



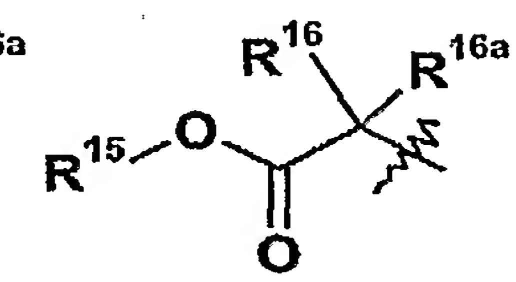
III-e



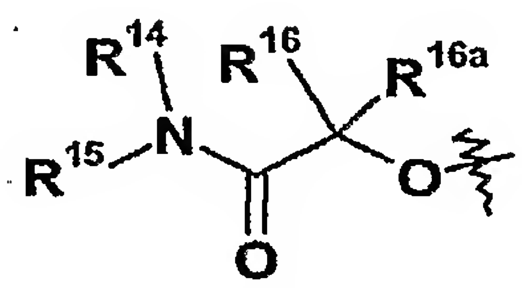
III-f



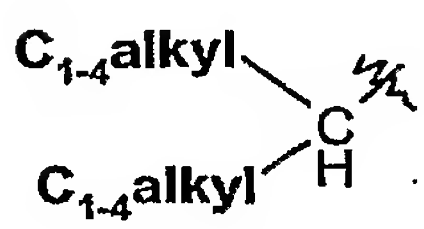
III-g



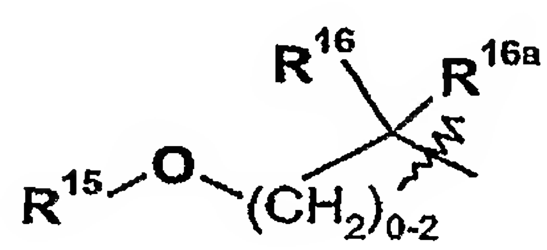
III-h



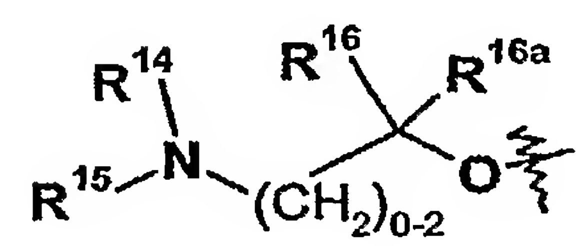
III-i



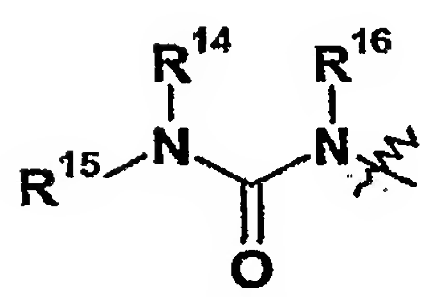
III-j



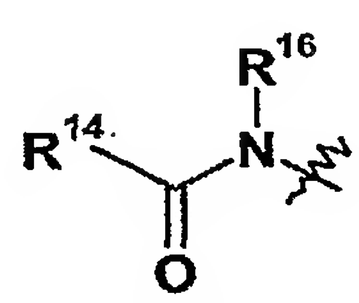
III-k



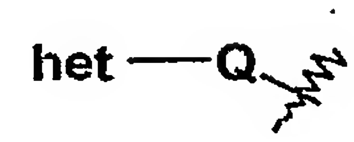
III-l



III-m



III-n



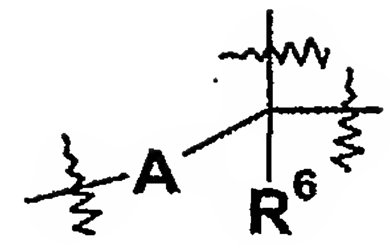
III-o

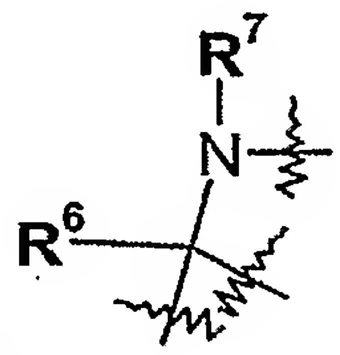
wherein:

het represents an optionally substituted 3- to 8-membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, wherein the optional substituents are selected from 1-2 groups selected from **R**^{12} and **R**^{13}; and

Q is selected from a direct bond or $-[C(\mathbf{R}^{16}\mathbf{R}^{16a})]_{1\text{-}2}-$

R^6 and **R**^{6a} are independently selected from hydrogen, fluoro, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or **R**^{6} and **R**^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms or **R**^{6} and **R**^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

$\mathbf{R^7}$ is selected from: hydrogen or C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from:

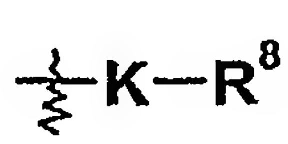
(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–S(O_n)-, -O-$\mathbf{R^b}$, –N$\mathbf{R^b}\mathbf{R^c}$, –C(O)-$\mathbf{R^b}$, –C(O)O-$\mathbf{R^b}$, -CON$\mathbf{R^b}\mathbf{R^c}$, NH-C(O)-$\mathbf{R^b}$ or –S(O_n)N$\mathbf{R^b}\mathbf{R^c}$,
where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by $\mathbf{R^{12}}$, or $\mathbf{R^{13}}$;

(iv) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by up to 4 substituents independently selected from $\mathbf{R^{12}}$ or $\mathbf{R^{13}}$;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ taken together can form an optionally substituted ring of 3-9 atoms, wherein the optional substituents are selected from $\mathbf{R^{12}}$ and


;

$\mathbf{R^{11}}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl or N($\mathbf{R^9}\mathbf{R^{10}}$);

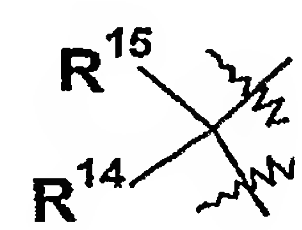
$\mathbf{R^{12}}$ is independently selected from: hydrogen, hydroxy, hydroxyC_{1-6}alkyl, oxo, cyano, cyanoC_{1-6}alkyl, nitro, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{0-2}alkyl, C_{1-6}alkoxycarbonylC_{0-2}alkyl, C_{1-6}alkanoylC_{0-2}alkyl, C_{1-6}alkanoyloxyC_{0-2}alkyl, C_{2-6}alkenyl, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, aryl, arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, N-C_{1-4}alkylaminoC_{0-2}alkyl, N, N-di-C_{1-4}alkylaminoC_{0-2}alkyl, N-C_{1-4}alkylcarbamoylC_{0-2}alkyl, N, N-di-C_{1-4}alkylaminocarbamoylC_{0-2}alkyl, N-C_{1-6}alkyaminocarbonylC_{0-2}alkyl, N, N-C_{1-6}alkyaminocarbonylC_{0-2}alkyl, C_{1-6}alkyl-$S(O)_n$-aminoC_{0-2}alkyl-, aryl-$S(O)_n$-aminoC_{0-2}alkyl-, C_{1-3}perfluoroalkyl-$S(O)_n$-aminoC_{0-2}alkyl-; C_{1-6}alkylamino-$S(O)_n$-C_{0-2}alkyl-, arylamino-$S(O)_n$-C_{0-2}alkyl-, C_{1-3}perfluoroalkylamino-$S(O)_n$-C_{0-2}alkyl-, C_{1-6}alkanoylamino-$S(O)_n$-C_{0-2}alkyl-; arylcarbonylamino-$S(O)_n$-C_{0-2}alkyl-, C_{1-6}alkyl-$S(O)_n$-C_{0-2}alkyl-, aryl-$S(O)_n$-C_{0-2}alkyl- , C_{1-3}perfluoroalkyl- or C_{1-3}perfluoroalkoxyC_{0-2}alkyl; wherein an amino group within $\mathbf{R^{12}}$ is optionally substituted by C_{1-4}alkyl;

$\mathbf{R^{13}}$ is C_{1-4}alkylaminocarbonyl optionally substituted by 1, 2 or 3 groups selected from $\mathbf{R^{12}}$;

$\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are selected from:

(i) $\mathbf{R^{14}}$ selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -$\mathbf{R^d}$-Ar, where $\mathbf{R^d}$ represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{15}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

(ii) wherein the group of Formula (III) represents a group of Formula **III-a** , **III-b**, **III-i**, **III-l** or **III-m**, then the group $NR^{14}(-R^{15})$ represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) wherein the group of Formula (III) represents structure **III-e**, 

represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ are independently selected from:

(i) hydrogen or optionally substituted C_{1-8}alkyl; or

(ii) R^{16} and R^{16a} together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

R^{17} is hydrogen or C_{1-4}alkyl;

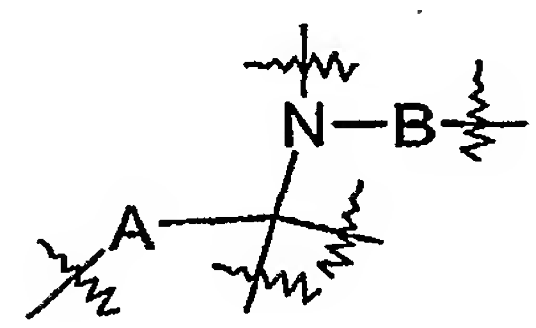
A is selected from:

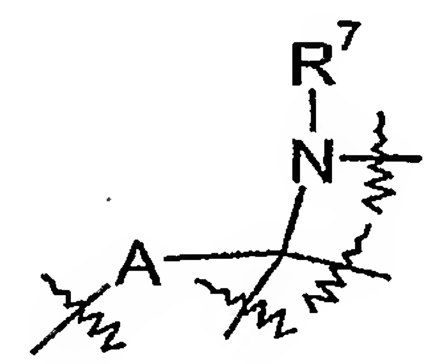
(i) a direct bond;

(ii) optionally substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, aryl or arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group or –C(O)–C(R^dR^d)-,. wherein R^d is independently selected from hydrogen and C_{1-2}alkyl;

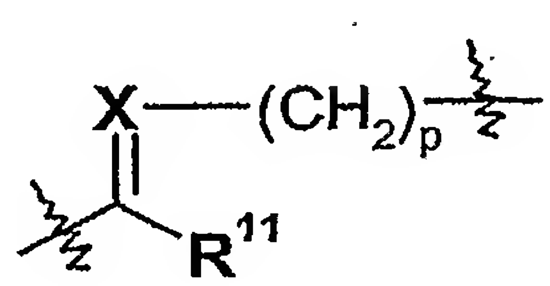
or when R^3 is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

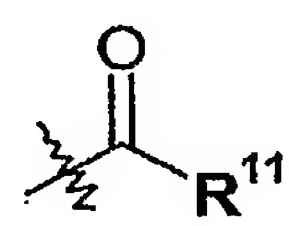
wherein:

X is selected from N or CH,

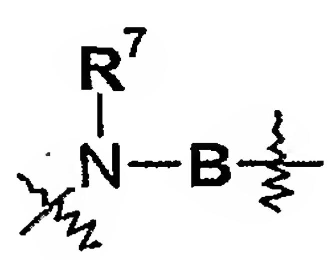
wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to R^8; and

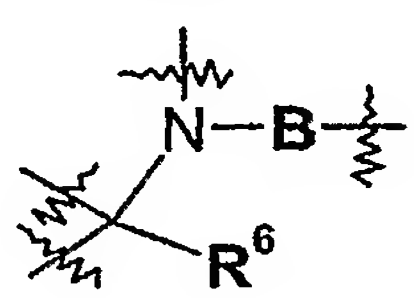
(iii) a group independently selected from: optionally substituted $C_{1\text{-}6}$alkylene, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted $C_{3\text{-}6}$alkenylene, optionally substituted $C_{3\text{-}6}$alkynyl, $(C_{1\text{-}5}alkyl)_{aa}$-$S(O_n)$-$(C_{1\text{-}5}alkyl)_{bb}$-, -$(C_{1\text{-}5}alkyl)_{aa}$-O-$(C_{1\text{-}5}alkyl)_{bb}$-, -$(C_{1\text{-}5}alkyl)_{aa}$-C(O)-$(C_{1\text{-}5}alkyl)_{bb}$- or $(C_{1\text{-}5}alkyl)_{aa}$-N($\mathbf{R}^{17}$)- $(C_{1\text{-}5}alkyl)_{bb}$, wherein $\mathbf{R}^{17}$ and the $(C_{1\text{-}5}alkyl)_{aa}$ or $(C_{1\text{-}5}alkyl)_{bb}$ chain can be joined to form a heterocyclic ring, wherein the combined length of $(C_{1\text{-}5}alkyl)_{aa}$ and $(C_{1\text{-}5}alkyl)_{bb}$ is less than or equal to C_5alkyl and wherein the optional substituents are independently selected from $\mathbf{R}^{12}$;

or the group –**B**-$\mathbf{R}^8$ represents a group of Formula (V)

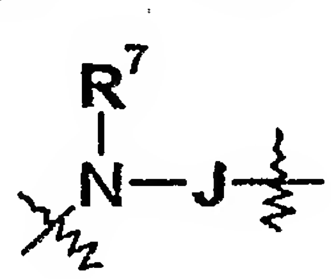


Formula (V);

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

J is a group of the formula: -$(CH_2)_s$-**L**-$(CH_2)_s$- or -$(CH_2)_s$-C(O)-$(CH_2)_s$-**L**-$(CH_2)_s$-wherein when **s** is greater than 0, the alkylene group is optionally substituted,

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$;

K is selected from: a direct bond, -$(CH_2)_{s1}$-, -$(CH_2)_{s1}$-O-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-C(O)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-$S(O_n)$-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-C(O)N($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)C(O)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)C(O)N($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-,

$-(CH_2)_{s1}$-OC(O)-$(CH_2)_{s2}$-, $-(CH_2)_{s1}$-C(O)O-$(CH_2)_{s2}$-, $-(CH_2)_{s1}$-N(**R**^{17})C(O)O-$(CH_2)_{s2}$-, $-(CH_2)_{s1}$-OC(O)N(**R**^{17})-$(CH_2)_{s2}$-, $-(CH_2)_{s1}$-OS(O_n)-$(CH_2)_{s2}$-, or $-(CH_2)_{s1}$-S(O_n)-O-$(CH_2)_{s2}$-, $-(CH_2)_{s1}$-S$(O)_2$N(**R**^{17})-$(CH_2)_{s2}$-or $-(CH_2)_{s1}$-N(**R**^{17})S$(O)_2$-$(CH_2)_{s2}$-; wherein the $-(CH_2)_{s1}$- and $-(CH_2)_{s2}$- groups are independently optionally substituted by hydroxy or C_{1-4}alkyl and wherein when s1>1 or s2>1 then the CH_2 group can optionally be a branched chain.;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

M is selected from $-CH_2$-CH_2- or –CH=CH-;

n is an integer from 0 to 2;

p is an integer from 0 to 4;

s, s1 and **s2** are independently selected from an integer from 0 to 4, and **s1+s2** is less than or equal to 4;

t is an integer between 0 and 4; and

or a salt, solvate or pro-drug thereof.

In a further embodiment of the invention there is a provided a compound of Formula (I) as defined above wherein:

R^{13} is –C(O)-**R**^{18};

R^{18} is selected from an amino acid derivative or an amide of an amino acid derivative;

or a salt, solvate or pro-drug thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I), or salt, pro-drug or solvate thereof:

(a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;

(b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

(c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl**, **alkylene**, **alkenyl** or **alkynyl** moiety may be linear or branched. The term "**alkylene**" refers to the group $-CH_2-$. Thus, C_8 alkylene for example is $-(CH_2)_8-$. For avoidance of doubt the term C_0alkyl within the group C_{0-5}alkyl is a direct bond.

The term '**propylene**' refers to trimethylene and the branched alkyl chains $-CH(CH_3)CH_2-$ and $-CH_2-CH(CH_3)-$. The straight chain propylene di-radical is preferred, i.e. $-CH_2CH_2CH_2-$. Specific propylene radicals refer to the particular structure, thus the term, propyl-2-ene refers to the group $-CH_2-CH(CH_3)-$. Similar notation is used for other divalent alkyl chains such as butylene.

The term '**2-propenyl**' refers to the group $-CH_2-CH=CH-$.

The term "**aryl**" refers to phenyl or naphthyl.

The term "**carbamoyl**" refers to the group $-C(O)NH_2$.

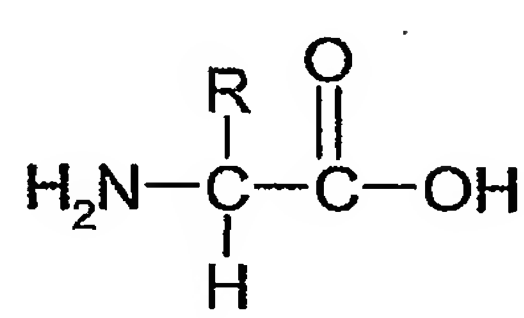
The term "**halo**" refers to fluoro, chloro, bromo or iodo.

The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 4-12 membered, preferably 5-10 membered aromatic mono or bicyclic ring or a 4-12 membered, preferably 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is

an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl, benzodioxyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O2) group.

The term "**aromatic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, pyrazolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include phenyl, thienyl and pyridyl.

The term **"amino acid residue"** is defined as that derived from the coupling of an L- or D-amino acid with a carboxyl group via an amide bond. This bond is formed via the amino group on the amino acid backbone. Amino acid residues include those derived from natural and non-natural amino acids, preferably natural amino acids and include α-amino acids β-amino acids and γ-amino acids. For the avoidance of doubt amino acids include those with the generic structure:



where R is the amino acid side chain. The definition of amino acid also includes amino acid analogues which have additional methylene groups within the amino acid backbone, for example β-alanine and amino acids which are not naturally occurring such as cyclohexylalanine.

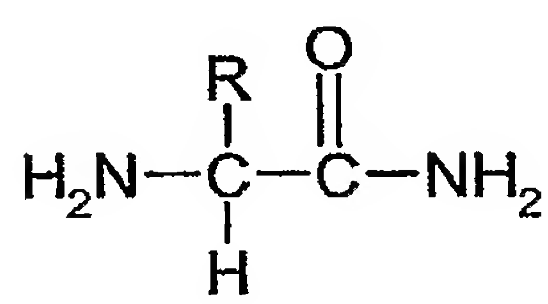
Preferred amino acids include glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparaginine, glutamine, aspartic acid, glutamic acid, lysine, histidine, β-alanine and ornithine. More preferred amino acids include glutamic acid, serine, threonine, glycine, alanine, β-alanine and

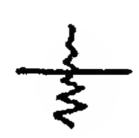
lysine. Yet more preferred amino acids include: alanine, asparagine, glycine, leucine, methionine, serine and threonine and non-natural amino acids with the following side chains: CH_3-S-CH_2-, CH_3-CH_2-, CH_3-CH(OH)- and HO-CH_2CH_2-.

Especially preferred amino acids include alanine, leucine, methionine and serine and non-natural amino acids with the following side chains: CH_3-S-CH_2-, CH_3-CH_2-, CH_3-CH(OH)- and HO-CH_2CH_2-.

An amide of an amino acid is defined as amino acid as defined above wherein the carboxy group on the amino acid backbone has been converted to an amide, or where present the carboxyl group on an amino acid side chain has been converted to an amide. Optionally the amino group of the amide group is substituted by C_{1-4}alkyl.

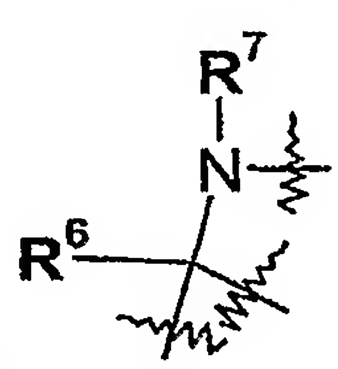
For example, the equivalent generic structure to the generic amino structure above is:

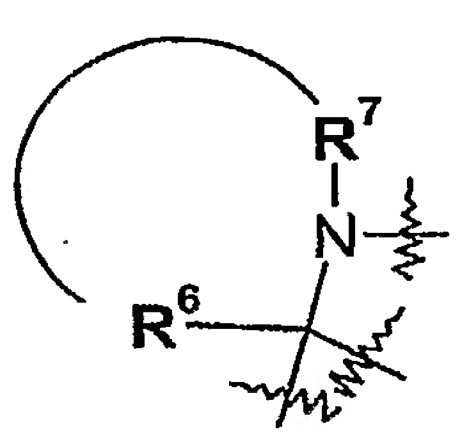


The symbol  denotes where the respective group is linked to the remainder of the molecule.

For the avoidance of doubt where two groups or integers appear within the same definition, for example, -$(CH_2)_s$-L-$(CH_2)_s$-, then these can be the same or different.

For the avoidance of doubt, where several groups together form a ring, for example:

'the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms', then the groups shown cyclises to form a ring, i.e

 the components of which are defined by the definitions of the groups which form the ring, thus in the above example the ring would include a nitrogen atom. For example in Example 5 this group forms a piperazine ring.

The term **C_{1-3}perfluoroalkyl** refers to a C_{1-3}alkyl chain in which all hydrogens have been replaced with a fluorine atom. Examples of **C_{1-3}perfluoroalkyl** include trifluoromethyl, pentafluoroethyl and 1-trifluoromethyl-1,2,2,2-tetrafluoroethyl. Preferably **C_{1-3}perfluoroalkyl** is trifluromethyl.

Examples of **C_{1-8}alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; examples of **C_{1-8}alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C_{1-6}alkenyl** include allyl (2-propenyl) and 2-butenyl, examples of **C_{1-6}alkynyl** include 2-propynyl and 3-butynyl, examples of **haloC_{1-6}alkyl** include fluoroethyl, chloropropyl and bromobutyl, examples of **hydroxyC_{1-6}alkyl** include hydroxymethyl, hydroxyethyl and hydroxybutyl, examples of **C_{1-8}alkoxy** include methoxy, ethoxy and butyloxy; examples of **C_{1-4}alkoxyC_{1-4}alkyl** include methoxyethyl, propoxybutyl and propoxymethyl, examples of **C_{1-6}alkanoyl** incude formyl, ethanoyl, propanoyl or pentanoyl, examples of **N-C_{1-4}alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C_{1-4}alkylamino** include N,N-dimethylaminoethyl, N,N-dimethylaminopropyl and N,N-dipropylaminoethyl, examples of **HO-C_{2-4}alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropylamino, examples of **HO-C_{2-4}alkyl-N(C_{1-4}alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropylamino, examples of **C_{1-6}alkyl-S(O_n)-** include methylthio, methylsulphinyl, ethylsulphinyl, ethylsulphonyl and propylsulphonyl, examples of **arylC_{1-6}alkyl** include benzyl, phenethyl and phenylbutyl, examples of **heterocyclylC_{1-6}alkyl** include pyrrolidin-1-yl ethyl, imidazolylethyl, pyridylmethyl and pyrimidinylethyl.

It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

Preferred compounds of Formula (I) are those wherein any one of the following or any combination of the following apply.

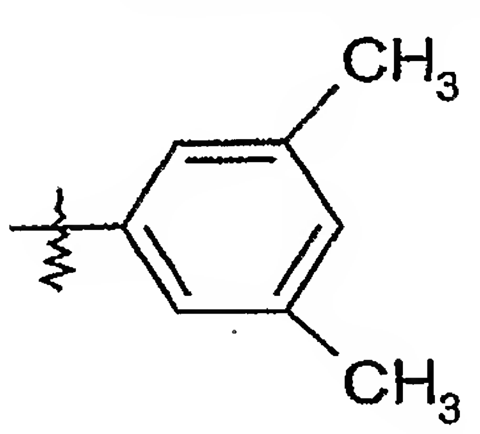
Preferably $\mathbf{R^1}$ is selected from hydrogen, optionally substituted C_{1-6}alkyl or optionally substituted arylC_{1-6}alkyl, wherein the optional substitutuents are as describes herein. More preferably $\mathbf{R^1}$ represents hydrogen, unsubstituted C_{1-6}alkyl or optionally substituted arylC_{1-6}alkyl. Yet more preferably $\mathbf{R^1}$ represents hydrogen, methyl, ethyl, *tert*-butyl or benzyl. Most preferably $\mathbf{R^1}$ represents hydrogen.

Preferably optional substituents on $\mathbf{R^1}$ are independently selected from: fluoro and C_{1-4}alkoxy. Most preferably $\mathbf{R^1}$ is unsubstituted.

Preferably $\mathbf{R^2}$ is an optionally substituted monocyclic aromatic ring structure, wherein the optional substitutuents are as described herein. Most preferably $\mathbf{R^2}$ represents optionally substituted phenyl, wherein the optional substitutuents are as described herein.

Preferably optional substituents on $\mathbf{R^2}$ are independently selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably optional substituents on $\mathbf{R^2}$ are independently selected from methyl, F or Cl. Preferably $\mathbf{R^2}$ bears 1, 2 or 3 substituents, most preferably 2 substituents.

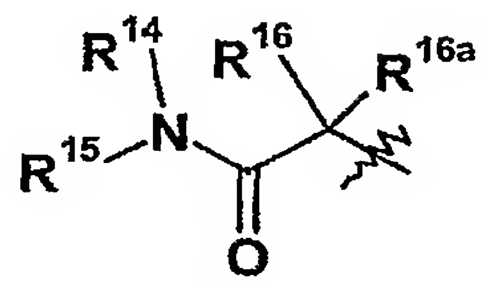
Most preferably $\mathbf{R^2}$ represents

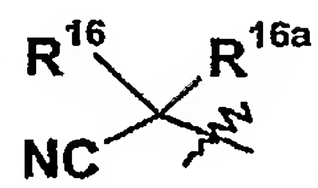


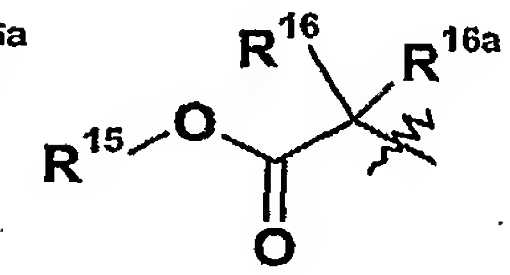
Preferably $\mathbf{R^3}$ is selected from a group of Formula (IIc) or Formula (IId). Most preferably $\mathbf{R^3}$ is a group of Formula (IId).

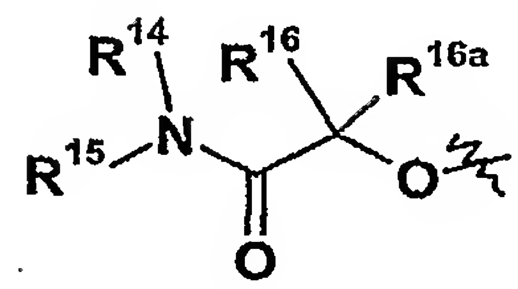
Preferably $\mathbf{R^4}$ is selected from hydrogen, methyl, ethyl, chloro or bromo. Further preferably $\mathbf{R^4}$ is selected from hydrogen or chloro. Most preferably $\mathbf{R^4}$ is hydrogen.

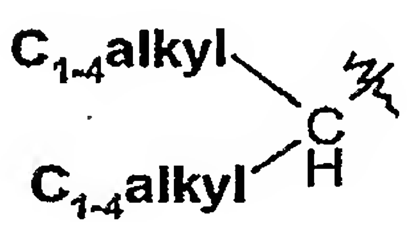
Preferably $\mathbf{R^5}$ is selected from a group of Formula **III-a** , **III-g, III-h, III-i, III-j, III-k** , **III-l**: or **III-o**

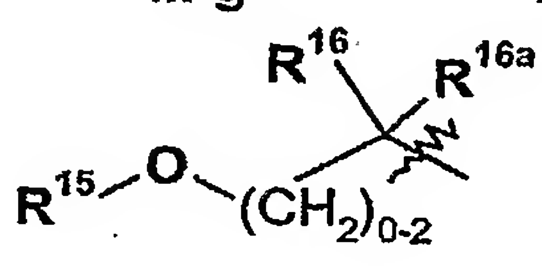

III-a

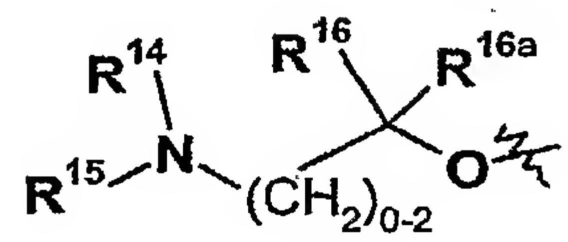

III-g

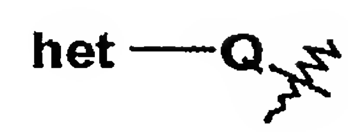

III-h


III-i


III-j

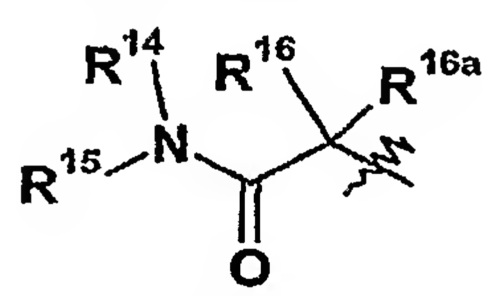

III-k

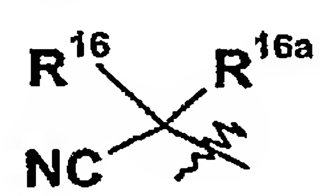

III-l

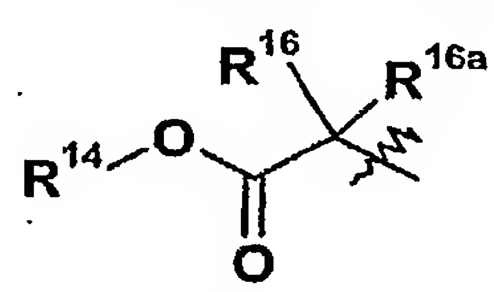

III-o

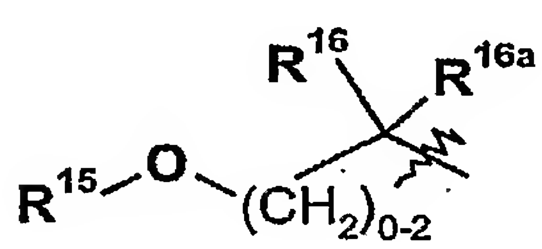
wherein $\mathbf{R^{16}}$, $\mathbf{R^{16a}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are as defined above.

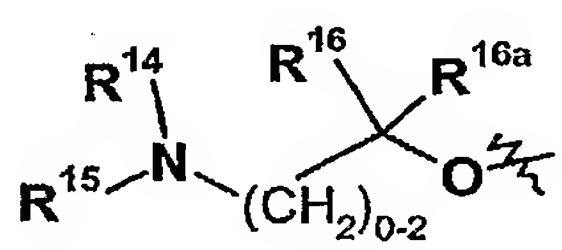
More preferably the group of Formula (III) is selected from one of the following groups:


III-a


III-g

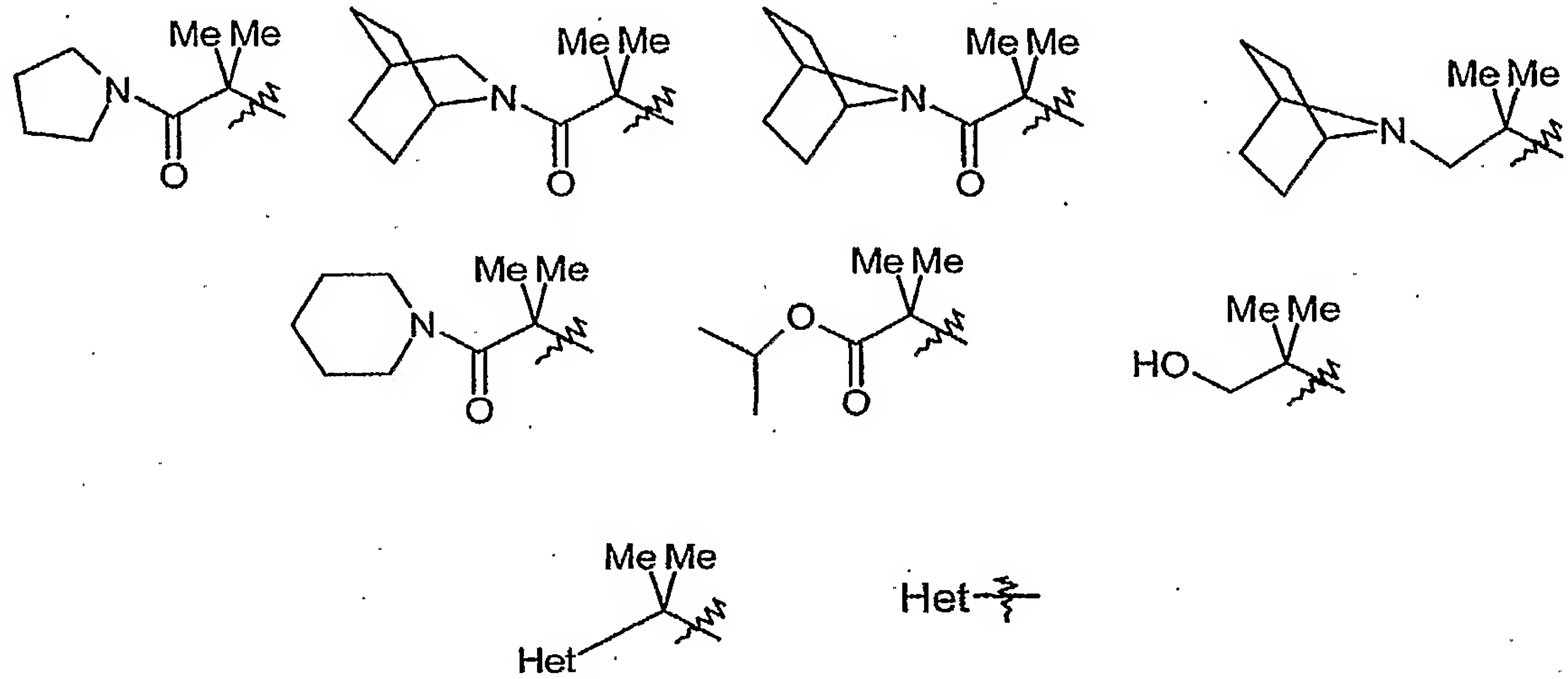

III-h


III-k


III-l

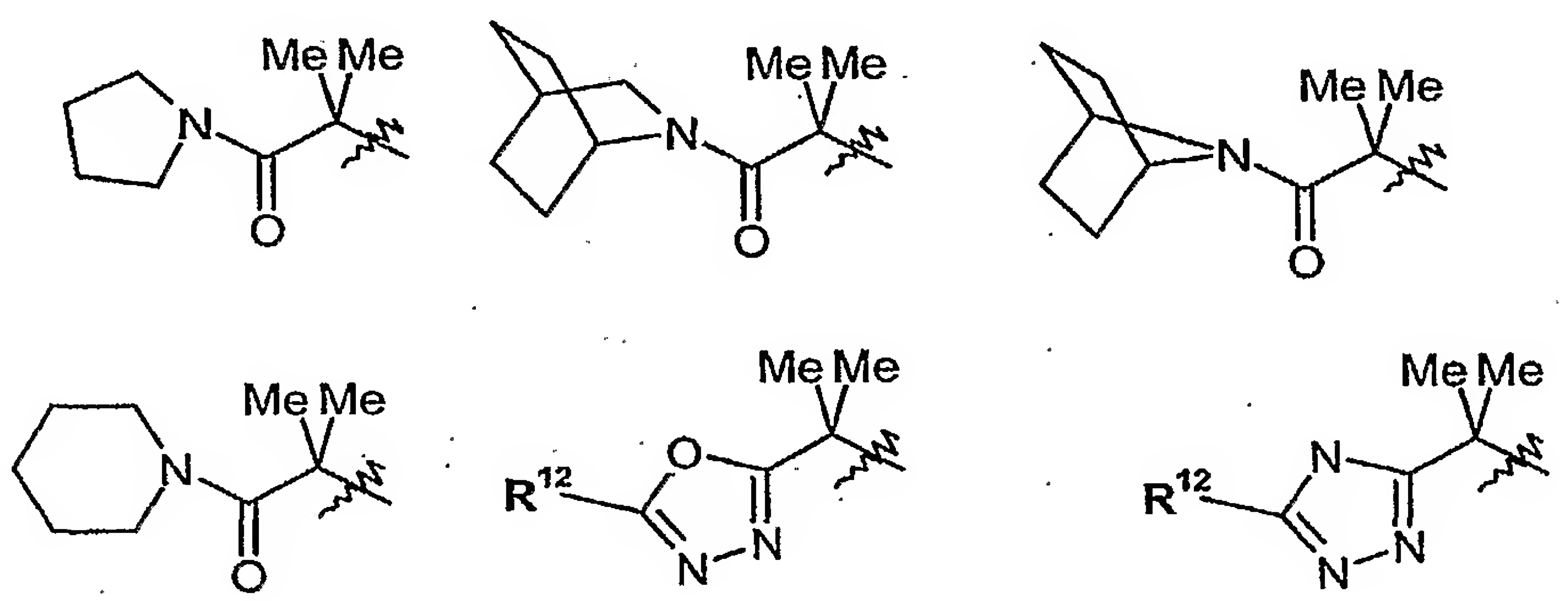
wherein $\mathbf{R^{16}}$, $\mathbf{R^{16a}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are as defined above.

Further preferably the group of Formula (III) is selected from one of the following groups:

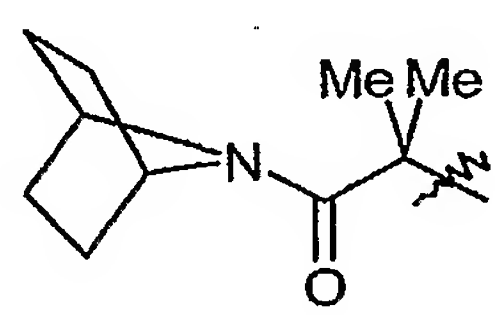


wherein Me represents methyl and het is as defined above.

Yet further preferably the group of Formula (III) is selected from one of the following groups:



Most preferably the group of Formula (III) is:



Preferably $\mathbf{R^6}$ **and** $\mathbf{R^{6a}}$ are independently selected from hydrogen, fluoro, optionally substituted C_{1-6}alkyl or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms More preferably $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are independently selected from hydrogen, unsubstituted C_{1-6}alkyl or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms. Yet more preferably $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are independently selected from hydrogen, methyl or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ taken together and

the carbon atom to which they are attached form cyclopropyl. Most preferably $\mathbf{R}^6$ is hydrogen and $\mathbf{R}^{6a}$ is methyl.

Preferably $\mathbf{R}^7$ is selected from: hydrogen or C_{1-4}alkyl. More preferably $\mathbf{R}^7$ is hydrogen or methyl. Most preferably $\mathbf{R}^7$ is hydrogen.

Preferably $\mathbf{R}^8$ is selected from

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, haloC_{1-6}alkyl, hydroxy, cyano, C_{1-6}alkylS(O_n)-, -O-$\mathbf{R}^b$, C_{1-4}alkoxyC_{1-4}alkyl, -C(O)-$\mathbf{R}^b$, C(O)O-$\mathbf{R}^b$, -NH-C(O)-$\mathbf{R}^b$, N,N-di-C_{1-4}alkylamino, -S(O_n)N$\mathbf{R}^b\mathbf{R}^c$

where $\mathbf{R}^b$ and $\mathbf{R}^c$ are independently selected from hydrogen and C_{1-6}alkyl, and **n** is 0, 1 or 2;

(ii) C_{4-7}heterocyclyl, optionally substituted by up to 3 groups selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$, more preferably $\mathbf{R}^8$ is selected from: azirinyl, azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, dioxanyl, trioxanyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl tetrahydrothiopyran, 1-oxotetrahydrothiopyran, 1,1-dioxotetrahydrothiopyran, dithianyl, trithianyl, morpholinyl, oxathiolanyl, oxathianyl, thiomorpholinyl, thiazinanyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, thiazolidinyl, pyrrolyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, thiazolyl, thiadiazolyl, thiadiazinyl, oxazolyl, isoxazolyl, oxadiazolyl, furazanyl, octahydropyrrolopyrrolyl, octahydropyrrolopyrrolyl,benzotriazolyl, dihydrobenzotriazolyl, indolyl, indolinyl, benzimidazolyl, 2,3-dihydrobenzimidazoly, benzotriazolyl 2,3-dihydro benzotriazolyl quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinozalinyl, naphthyridinyl, pteridinyl, benzodioxolyl, tetrahydrodioxolopyrrolyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl or 8-oxa-3-azabicyclooctanyl; each of which is optionally substituted by up to 3 groups selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$ or

(iii) phenyl or C_{3-7}carbocyclyl; each of which is optionally substituted by up to 3 groups selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$;

Further preferably $\mathbf{R}^8$ is selected from

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, haloC_{1-6}alkyl, hydroxy, cyano, C_{1-6}alkylS(O_n)-, -O-$\mathbf{R}^b$, C_{1-4}alkoxyC_{1-4}alkyl, -C(O)-$\mathbf{R}^b$, C(O)O-$\mathbf{R}^b$, -NH-C(O)-$\mathbf{R}^b$, N,N-di-C_{1-4}alkylamino, -S(O_n)N$\mathbf{R}^b\mathbf{R}^c$

where R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, and **n** is 0, 1 or 2;

preferably selected from: hydrogen, methyl, isopropyl, *t*-butyl, 1-methylethyl, allyl, fluoroethyl, hydroxy, cyano, ethylsulphonyl, methoxy, 1-methyl-2-methoxyethyl, acetyl, t-butoxycarbonyl, acetylamino, dimethylamino, diethylamino, (1-methylethyl)amino, isopropylamino or aminosulphonyl;

(ii) azetidinyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, morpholinyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, imidazolyl, triazolyl, thienyl, thiazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, benzodioxolyl, 2,3-dihydrobenzotriazolyl, 1,2-dihydroquinolinyl or octahydropyrrolo[3,4-c]pyrrolyl; each of which is optionally substituted by up to 3 groups selected from R^{12} and R^{13}; or

(iii) phenyl or C_{3-7}carbocyclyl, each of which is optionally substituted by up to 3 groups selected from R^{12} and R^{13};

Yet further preferably R^8 is selected from

(i) phenyl optionally substituted by up to 3 groups selected from R^{12} and R^{13} or naphthyl;

(ii) furanyl, tetrahydropyranyl, pyrrolidinyl, piperazinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, thienyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, benzodioxolyl, 1,2-dihydroquinolinyl or 2,3-dihydrobenzotriazolyl; each of which is optionally substituted by up to 3 groups selected from R^{12} and R^{13};or

(iii) C_{3-7}carbocyclyl (preferably cyclohexyl or cylopentyl, more preferably cyclohexyl) optionally substituted by up to 3 groups selected from R^{12} and R^{13};

Further preferably R^8 is selected from: phenyl, morpholino, piperidino, thienyl, pyridyl and benzodioxlyl optionally substituted by up to 3 groups selected from R^{12} and R^{13}.

Further preferably R^8 is phenyl, morpholino, pyridyl, pyrrolidino, piperidino or 1,1-dioxo-isothiazolidin-2-yl or N-isopropylureido. Most preferably R^8 is phenyl.

More preferably optional substituents on R^8 are selected from: cyano, hydroxy, oxo, nitro, halo, trifluromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, $R^9OC(O)(CH_2)_w$-,

$R^9R^{10}N(CH_2)_w$-, $R^9R^{10}NC(O)(CH_2)_w$-, $R^9R^{10}NC(O)(CH_2)_w$-, $R^9R^{10}NC(O)N(R^9)(CH_2)_w$-, $R^9OC(O)N(R^9)(CH_2)_w$-, or halo, wherein **w** is an integer between 0 and 4 and R^9 and R^{10} are selected from: hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulphonyl and C_{3-7}carbocyclyl..

Further preferably optional substituents on R^8 are selected from: cyano, hydroxy, oxo, amino, N,N-diC_{1-4}alkyamino, N,N-diC_{1-4}alkyaminoC_{1-4}alkyl, N'-C_{1-4}alkylureido, N-C_{1-4}alkylsulphonylamino, N,N-di-C_{1-4}alkylsulphonylamino, nitro, halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C1-4alkoxycarbonylamino and C_{3-7}carbocyclylcarbonylamino.

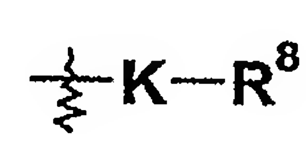
More preferably optional substituents on R^8 are selected from: cyano, hydroxy, oxo, methyl, ethyl, *t*-butyl, methoxy, acetyl, amino, N,N-dimethylamino, N'-isopropylureido, N'-cyclohexylureido, N-methylsulphonylamino, N,N-dimethylsulphonylamino, nitro, chloro, fluoro, trifluoromethyl, isopropoxycarbonylamino and cyclopentylcarbonylamino.

Further preferably optional substituents on R^8 are selected from: hydroxy, methyl, ethyl, methoxy, fluoro, methylsulphonylamino, isopropylureido and isopropoxycarbonylamino. Most preferably optional substituents on R^8 are selected from: methylsulphonylamino, isopropylureido and isopropoxycarbonylamino.

In a further embodiment of the invention optional substituents on R^8 are selected from: C_{1-4}alkoxy, fluoro, C_{1-4}alkylsulphonylamino, C_{1-4}alkanoylamino, C_{1-4}alkylureido and C_{1-4}alkoxycarbonylamino.

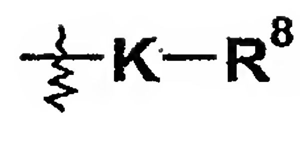
In a further embodiment of the invention when R^8 is phenyl then R^8 is preferably substituted and when R^8 is a heterocyclic ring R^8 is preferably unsubstituted.

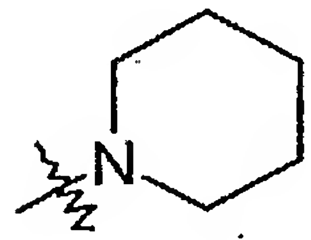
When R^9 is a C_{1-6}alkyl group substituted by an optionally substituted 3 to 10 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, the heterocyclic ring is preferably selected from pyridyl, thienyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, pyrrolidinyl, piperazinyl, morpholinyl, imidazolinyl, benztriazolyl, benzimidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, pyrrolyl, 1,3-dioxolanyl, 2-azetinyl, each of which is optionally substituted, wherein the optional substituents are preferably selected from R^{12} and



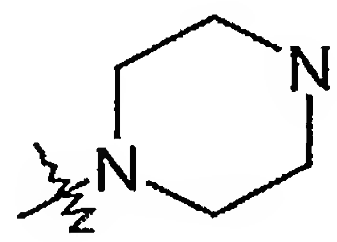
;

Further preferably the heterocyclic ring is a group of formula **VI-a, VI-b, VI-c, VI-d, VI-e, VI-f , VI-g, VI-h, VI-i, VI-j** or **VI-k**:, wherein each group is optionally substituted by one or more groups selected from R^{12} and

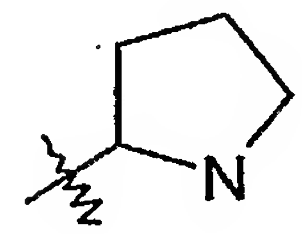




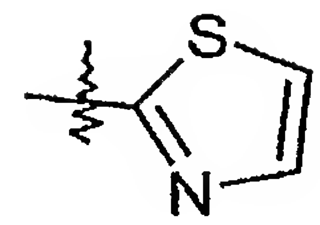
VI-a



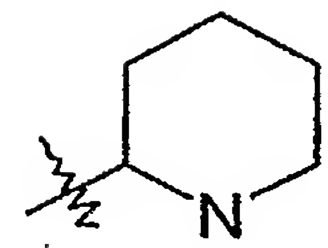
VI-b



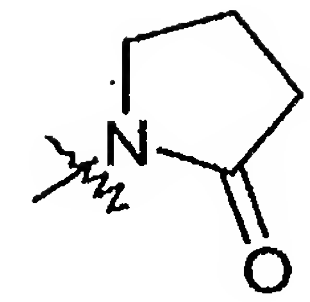
VI-c



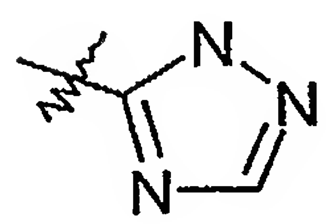
VI-d



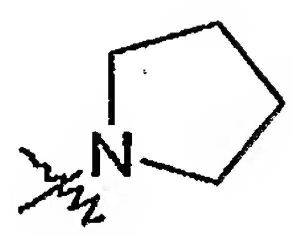
VI-e



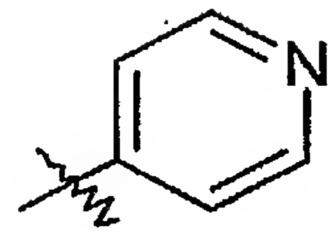
VI-f



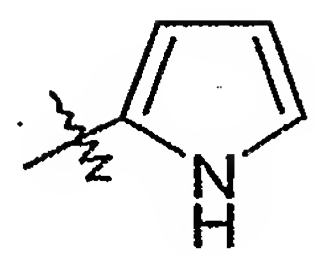
VI-g



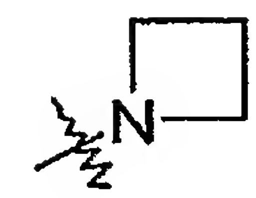
VI-h



VI-i

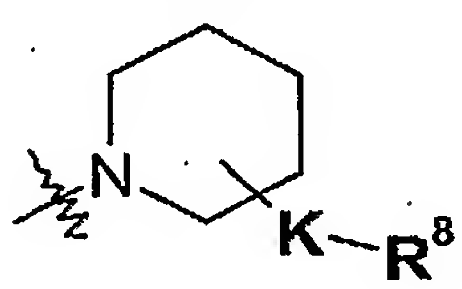


VI-j

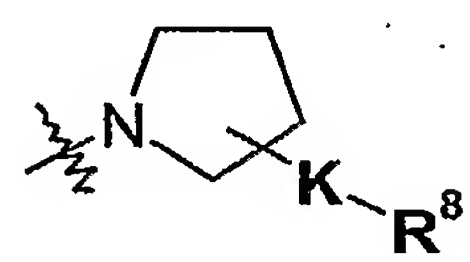


VI-k

Most preferably the heterocyclic ring is a group of formula **VI-a** or **VI-h**, wherein each group is optionally substituted by one or more groups selected from $\mathbf{R}^{12}$;



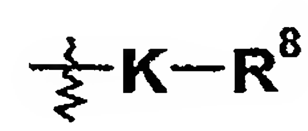
VI-a



VI-h

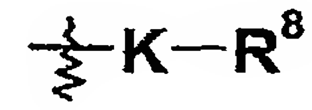
Preferably $\mathbf{R}^{10}$ comprises part of the group $N(\mathbf{R}^9\mathbf{R}^{10})$ or is optionally substituted C_{1-6}alkyl. Further preferably $\mathbf{R}^{10}$ comprises part of the group $N(\mathbf{R}^9\mathbf{R}^{10})$ or is selected from: methyl, ethyl or *tert*-butyl. Most preferably $\mathbf{R}^{10}$ comprises part of the group $N(\mathbf{R}^9\mathbf{R}^{10})$.

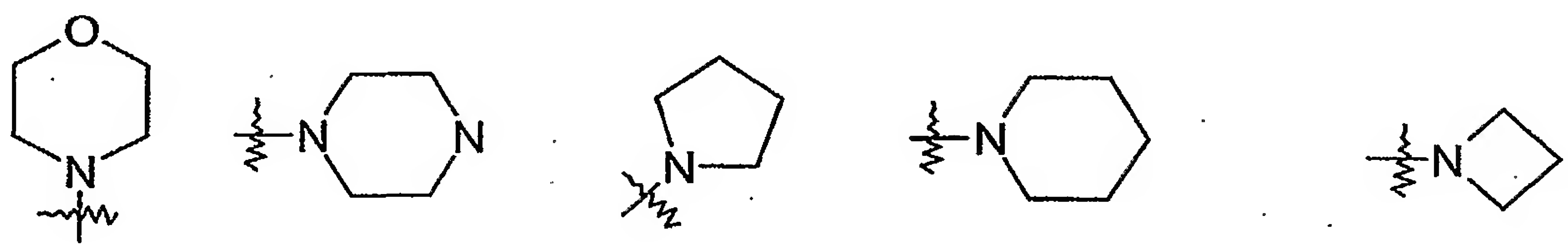
When $N(\mathbf{R}^9\mathbf{R}^{10})$ represents an optionally substituted 3- to 10-membered heterocyclic ring, $N(\mathbf{R}^9\mathbf{R}^{10})$ is preferably selected from a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S, wherein the optional substituents are independently selected from $\mathbf{R}^{12}$ and



Further preferably a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S selected from pyrrolidinyl, thienyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl piperazinyl, imidazole, or azetidinyl, wherein the optional substituents are independently selected from $\mathbf{R}^{12}$ and

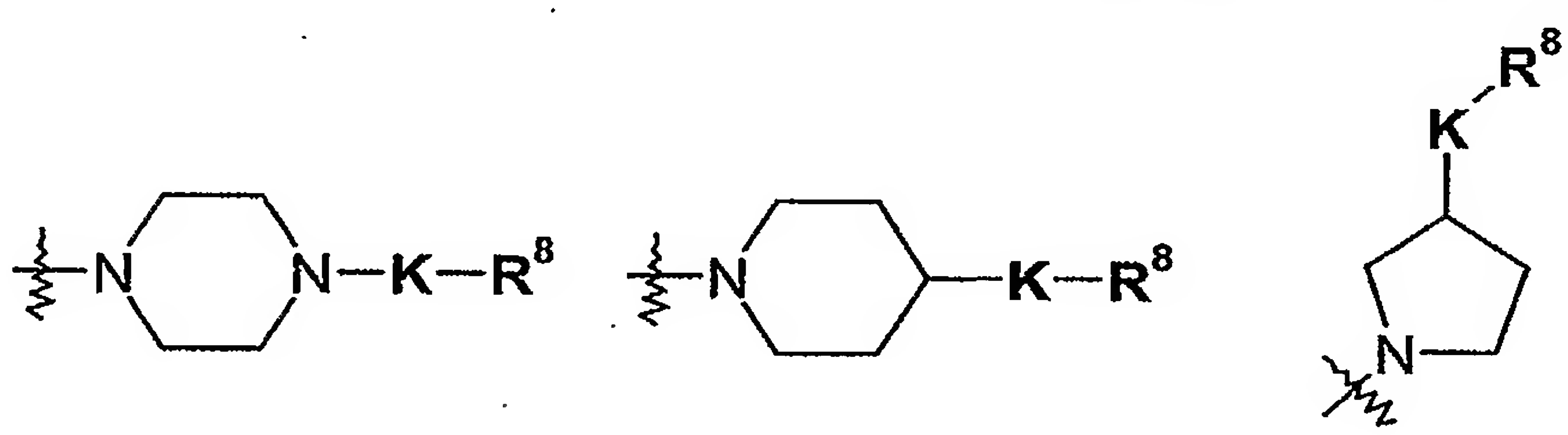
Further preferably the structure $N(\mathbf{R^9R^{10}})$ is a heterocyclic ring selected from an optionally substituted group of formula, **IV-a**, **IV-b**, **IV-c**, **IV-d** and **IV-e**, wherein each group is optionally substituted by one or more groups selected from $\mathbf{R^{12}}$ and





IV-a IV-b IV-c IV-d IV-e

Further preferably the structure $N(\mathbf{R^9R^{10}})$ is selected from a group of formula **Va**, **Vb** or **Vc**, wherein each group is optionally substituted by one or more groups selected from $\mathbf{R^{12}}$.



V-a V-b V-c

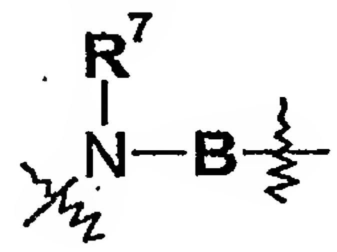
Most preferably the structure $N(\mathbf{R^9R^{10}})$ is a group of formula **V-b** or **V-c**, wherein each group is optionally substituted by one or more groups selected from $\mathbf{R^{12}}$.

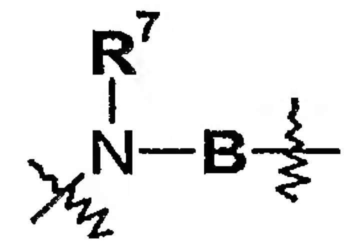
Preferably $\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ are independently selected from hydrogen and $C_{1\text{-}4}$alkyl. More preferably $\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ are independently selected from hydrogen, methyl and ethyl. Most preferably $\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ are both methyl.

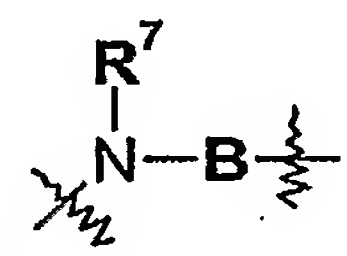
Preferably $\mathbf{R^{17}}$ is hydrogen or methyl. Most preferably $\mathbf{R^{17}}$ is hydrogen.

Preferably **A** is selected from a direct bond, optionally substituted $C_{1\text{-}5}$alkylene, carbonyl or $-C(O)-C(\mathbf{R^dR^d})-$, wherein $\mathbf{R^d}$ is independently selected from hydrogen and $C_{1\text{-}2}$alkyl, and wherein the optional substituents are independently selected from: hydroxy, hydroxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkyl, aryl or aryl$C_{1\text{-}6}$alkyl

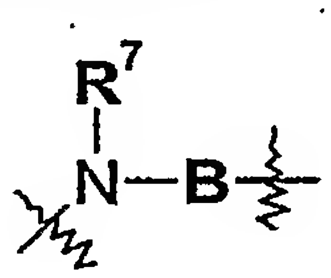
Further preferably **A** is selected from $C_{1\text{-}5}$alkylene optionally substituted with $C_{1\text{-}4}$alkyl or $C_{1\text{-}4}$alkoxy, carbonyl or carbonylmethyl. Yet further preferably **A** is a direct bond or methylene. Most preferably **A** is methylene.

Preferably **B** is selected from optionally substituted C_{1-6}alkylene, optionally substituted C_{3-6}alkenylene, -(C_{1-5}alkyl)$_{aa}$-O-(C_{1-5}alkyl)$_{bb}$, -(C_{1-5}alkyl)$_{aa}$-C(O)-(C_{1-5}alkyl)$_{bb}$-, -(CH_2)$_{s1}$-C(O)N(**R**^{17})-(CH_2)$_{s2}$-, or the group  forms an optionally substituted C_{4-7}heterocyclic ring, wherein **aa** and **bb** are independently 0 to 1.

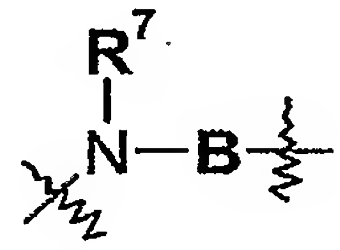
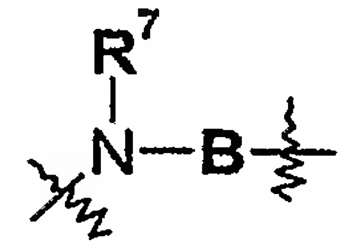
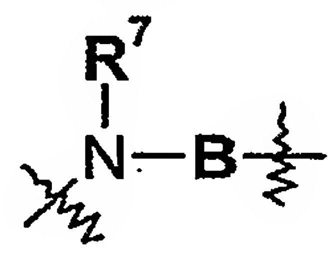
More preferably **B** is C_{1-6}alkylene, C_{3-6}alkenylene ,-(C_{1-5}alkyl)$_{aa}$-O-(C_{1-5}alkyl)$_{bb}$-, -(C_{1-5}alkyl)$_{aa}$-C(O)-(C_{1-5}alkyl)$_{bb}$-, -(CH_2)$_{s1}$-C(O)N(**R**^{9})-, or the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring, wherein **aa** and **bb** are independently 0 or 1 and wherein C_{1-6}alkylene is optionally substituted by hydroxy.

Further preferably **B** is unsubstituted C_{1-6}alkylene, C_{3-6}alkenylene -(C_{1-5}alkyl)$_{aa}$-O-(C_{1-5}alkyl)$_{bb}$-, -(C_{1-5}alkyl)$_{aa}$-C(O)- or the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring selected from: azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, thiazolidinyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from: cyano, hydroxy, oxo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, **R**^{16}OC(O)(CH_2)$_w$-, **R**^{16}**R**^{16a}NC(O)(CH_2)$_w$- or halo, wherein **w** is an integer between 0 and 4 and **R**^{16} and **R**^{16a} are as defined above. Further preferably the optional substituents are selected from: cyano, hydroxy, oxo, C_{1-4}alkyl, C_{1-4}alkoxy and C_{1-4}alkanoyl, **aa** and **bb** are independently 0 or 1, and wherein C_{1-6}alkylene is optionally substituted by hydroxy.

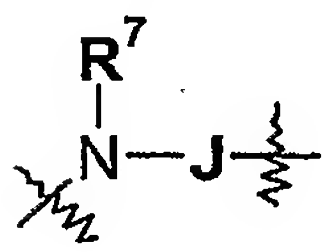
Yet further preferably **B** is selected from: methylene, ethylene, propylene, propyl-2-ene, butylene, pentylene, 2-propenyl, propoxy, ethoxyethyl, methylcarbonyl or methylcarbonylamino.

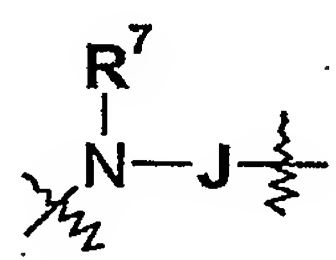
or the group  forms a C_{4-7}heterocyclic ring selected from:pyrrolidinyl, piperidinyl, or piperazinyl, wherein the optional substituents are selected from oxo.

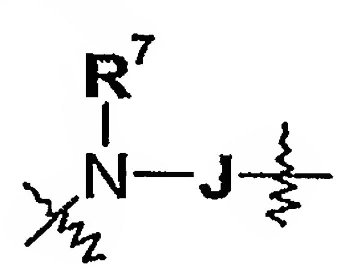
Most preferably **B** is selected from ethylene or butylene.

In another embodiment of the invention preferably **B** is selected from optionally substituted C_{1-6}alkylene or the group  forms a C_{5-7}heterocyclic ring. Preferably **B** is selected from unsubstituted C_{1-6}alkylene or the group  forms a saturated C_{5-7}heterocyclic ring. Most preferably **B** is selected from methylene, ethylene, propylene, butylene or or the group  forms a saturated C_{5-7}heterocyclic ring selected from piperidinyl or piperazinyl.

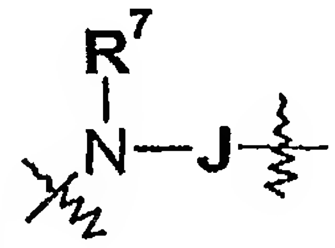
Preferably **M** is $-CH_2-CH_2-$.

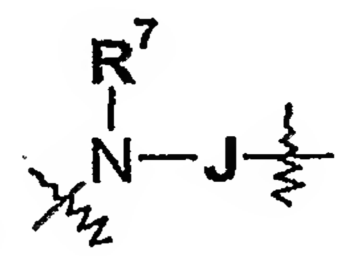
When $\mathbf{R}^3$ is selected from a group of Formula (IIc) or Formula (IId) then the group  preferably forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$.

More preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$.

Further preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring selected from: azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, morpholinyl,

thiomorpholinyl, thiazinanyl, thiazolidinyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from oxo, C_{1-4}alkyl and C_{1-4}alkoxy.

Further preferably the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring selected from: pyrrolidinyl, piperidinyl or piperazinyl, wherein the optional substituents are selected from C_{1-4}alkoxy, oxo and C_{1-4}alkyl.

Most preferably the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring selected from: piperazinyl or piperdinyl.

Preferably **K** is selected from: a direct bond, $-(CH_2)_s-$, $-(CH_2)_s-O-(CH_2)_s-$, $-(CH_2)_s-C(O)-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R^{17}})-(CH_2)_s-$, $-(CH_2)_s-C(O)N(\mathbf{R^{17}})-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R^{17}})C(O)-(CH_2)_s-$, $-(CH_2)_s-S(O)_2N(\mathbf{R^{17}})-(CH_2)_s-$, or $-(CH_2)_s-NHS(O)_2-(CH_2)_s-$, wherein **s** is independently selected from 0,1,2,3 or 4, $\mathbf{R^{17}}$ is selected from hydrogen or C_{1-4}alkyl (preferably hydrogen) and the $-(CH_2)_s-$ group is optionally substituted by hydroxy or C_{1-4}alkyl.

More preferably **K** is selected from: a direct bond, $-(CH_2)_s-$, $-(CH_2)_s-O-(CH_2)_s-$, $-(CH_2)_s-C(O)-$, $-C(O)-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R^{17}})-$, $-(CH_2)_s-C(O)N(\mathbf{R^{17}})-$, $-(CH_2)_s-N(\mathbf{R^{17}})C(O)-(CH_2)_s-$, $-(CH_2)_s-S(O)_2N(\mathbf{R^{17}})-$ or $-(CH_2)_s-NHS(O)_2-$, wherein **s** is independently selected from 0,1,2,3 or 4, $\mathbf{R^{17}}$ is selected from hydrogen or C_{1-4}alkyl (preferably hydrogen or methyl) and the $-(CH_2)_s-$ group is optionally substituted by hydroxy or C_{1-4}alkyl.

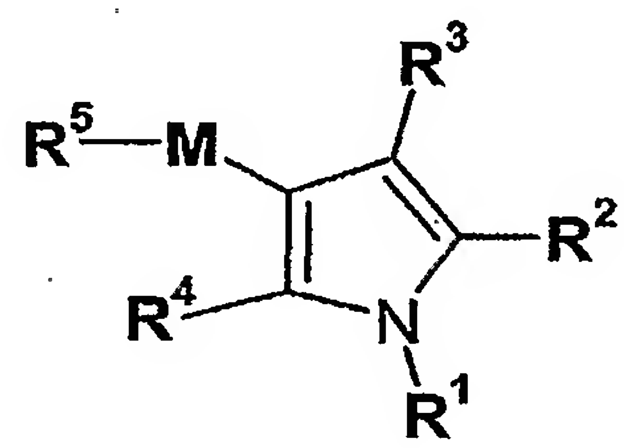
More preferably **K** is selected from: a direct bond, methylene, ethylene, propylene, butylene, oxy, 2-hydroxypropylene, carbonyl, methylcarbonyl, ethylcarbonyl, (methyl)methylcarbonyl, (ethyl)methylcarbonyl, carbonylmethylene, carbonylethylene, ethoxyethylene, amino, 2-hydroxypropylamino, carbonylamino, methylcarbonylamino, N-methyl-methylcarbonylamino, aminocarbonyl, methylaminocarbonyl, methylaminocarbonylmethyl, propylsulphonylamino or methylaminosulphonyl.

Further preferably **K** is selected from: a direct bond, methylene, ethylene, propylene, butylene carbonyl, methylcarbonyl or N-methylmethylcarbonylamino.

Further preferably **K** is selected from: a direct bond, methyl, carbonyl and methylcarbonyl.

In preferences for heterocyclyl in **R^8** the nitrogen atoms contained in **R^8** heteroaromatic rings exist either as drawn or, where chemically allowed, in their oxidised (N→O, N-OH) state.

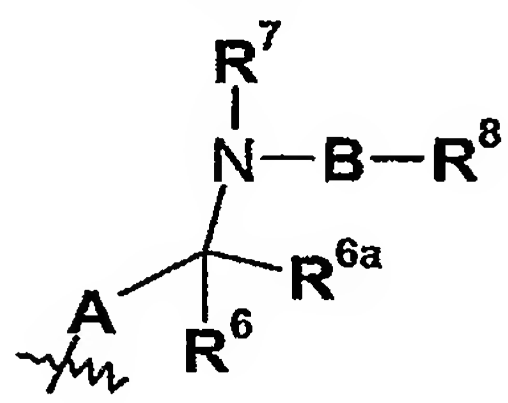
According to a further aspect of the invention there is provided a compound of Formula (Ia)



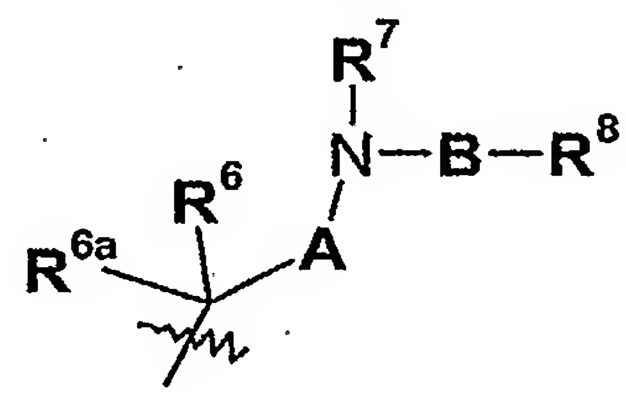
Formula (Ia)

wherein:

R^3 is selected from a group of Formula (IIa) or Formula (IIb):



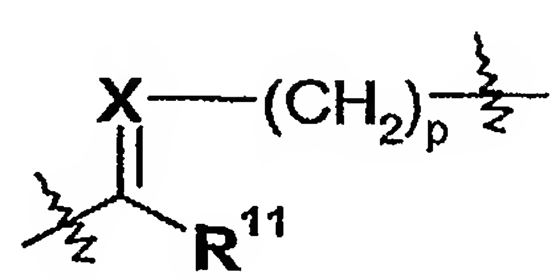
Formula (IIa)



Formula (IIb)

R^7 is selected from: hydrogen or C_{1-6}alkyl;

B is a group of Formula (IV)



Formula (IV)

and **A**, **M**, **R^1**, **R^2**, **R^4**, **R^5** **R^6**, **R^{6a}**, **R^8**, and **R^{11}** are as defined above for a compound of Formula (I)

or a salt, solvate or pro-drug thereof.

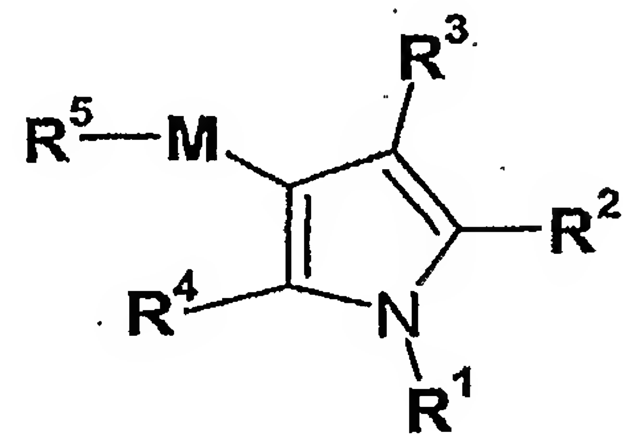
According to a further aspect of the invention there is provided a compound of Formula (Ia) wherein:

X is N;

R^8 is –C(O)O-**R^b**, wherein **R^b** is as defined above;

or a salt, solvate or pro-drug thereof.

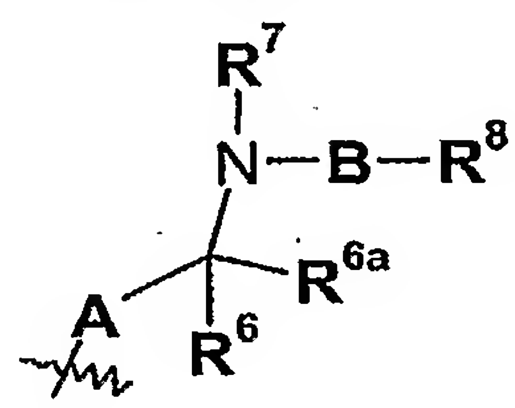
According to a further aspect of the invention there is provided a compound of Formula (Ib)



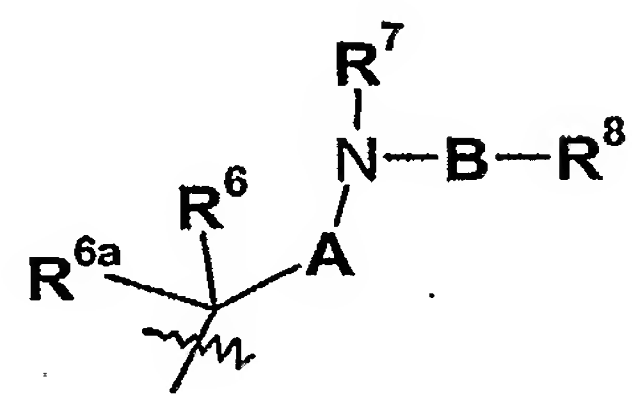
Formula (Ib)

wherein:

$\mathbf{R}^3$ is selected from a group of Formula (IIa) or Formula (IIb):

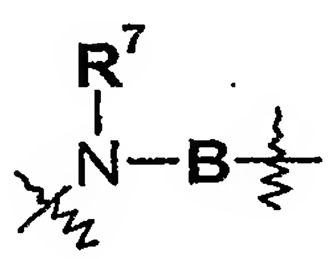


Formula (IIa)



Formula (IIb)

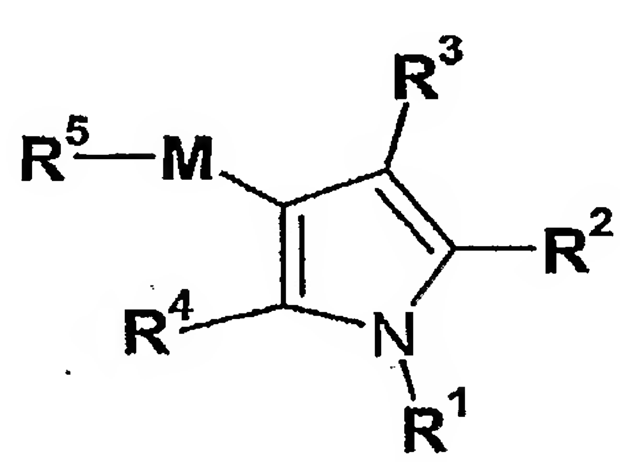
wherein

the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$;

and **A**, **M**, **B**, $\mathbf{R}^1$, $\mathbf{R}^2$, $\mathbf{R}^4$, $\mathbf{R}^5$ $\mathbf{R}^6$, $\mathbf{R}^{6a}$, $\mathbf{R}^8$, $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$ are as defined above for a compound of Formula (I)

or a salt, solvate or pro-drug thereof.

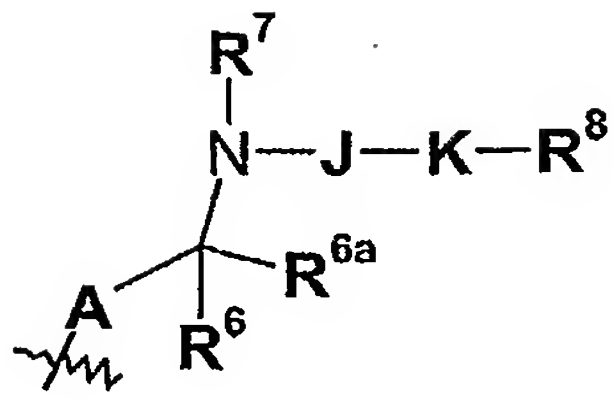
According to a further aspect of the invention there is provided a compound of Formula (Ic)



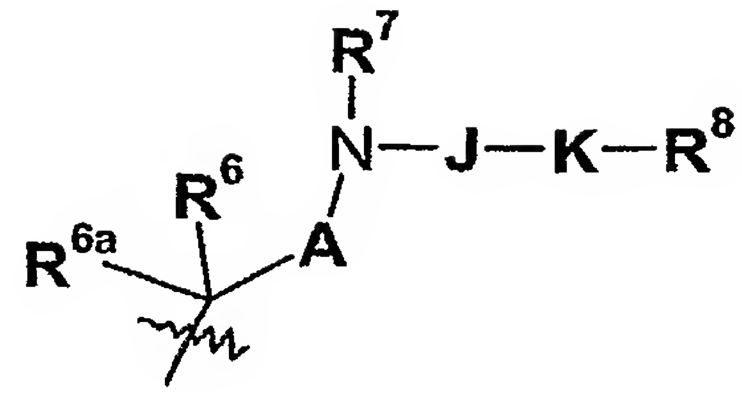
Formula (Ic)

wherein:

$\mathbf{R}^3$ is selected from a group of Formula (IIc) or Formula (IId):

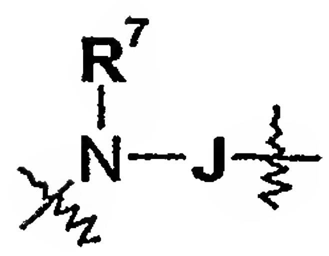


Formula (IIc)



Formula (IId)

wherein

the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from **R**^{12} and **R**^{13};

and **A, M, J, R**^{1}, **R**^{2}, **R**^{4}, **R**^{5} **R**^{6}, **R**^{6a}, **R**^{8}, and **R**^{12} and **R**^{13} are as defined above for a compound of Formula (I)

or a salt, solvate or pro-drug thereof.

According to a further aspect of the invention there is provided a compound of Formula (Ic), wherein:

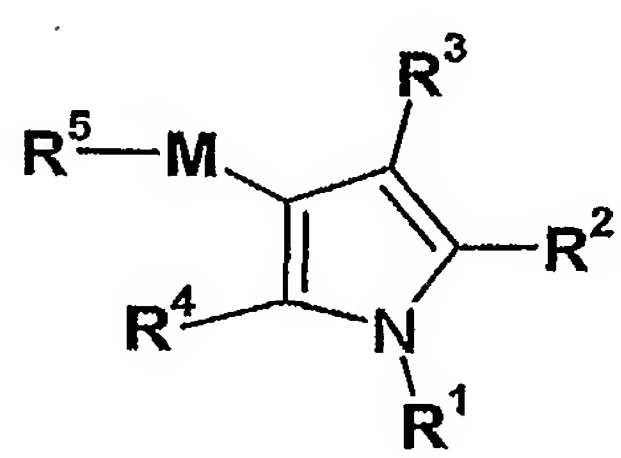
K is -$(CH_2)_{s1}$-C(O)-$(CH_2)_{s2}$- or -$(CH_2)_{s1}$-;

R^{8} is selected from: $C_{3\text{-}7}$cycloalkyl, aryl or heterocyclyl each of which is optionally substituted by one or substituents independently selected from **R**^{12} or **R**^{13}; and

s1 and **s2** are as defined above;

or a salt, solvate or pro-drug thereof.

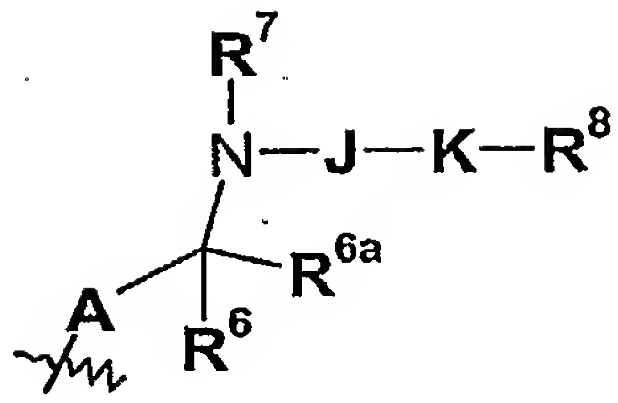
According to a further aspect of the invention there is provided a compound of Formula (Id)



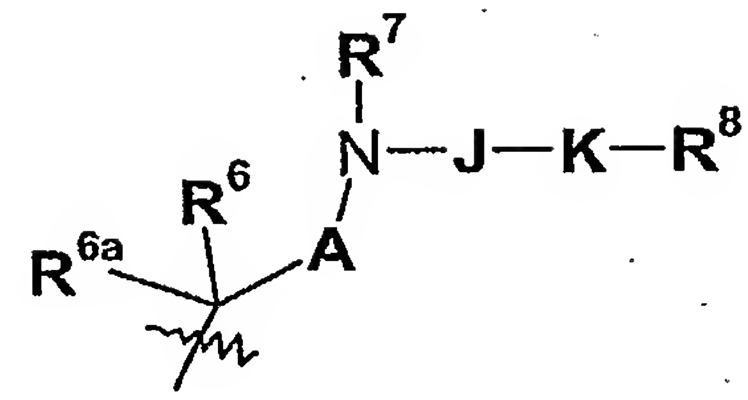
Formula (Id)

wherein:

R^{3} is selected from a group of Formula (IIc) or Formula (IId):



Formula (IIc)



Formula (IId)

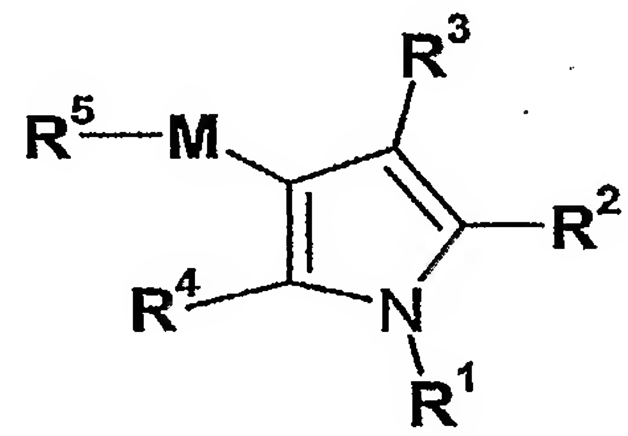
wherein

J is a group of the formula: -$(CH_2)_s$-**L**-$(CH_2)_s$- or -$(CH_2)_s$-C(O)-$(CH_2)_s$-**L**-$(CH_2)_s$-wherein when **s** is greater than 0, the alkylene group is optionally substituted by 1 to 2 group selected from $\mathbf{R^{12}}$,

and **A**, **K**, **L**, **M**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^4}$, $\mathbf{R^5}$ $\mathbf{R^6}$, $\mathbf{R^{6a}}$, $\mathbf{R^8}$, and $\mathbf{R^{12}}$ are as defined above for a compound of Formula (I)

or a salt, solvate or pro-drug thereof.

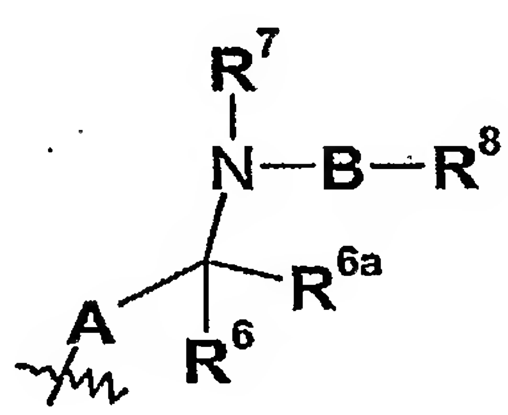
According to a further aspect of the invention there is provided a compound of Formula (Ie)



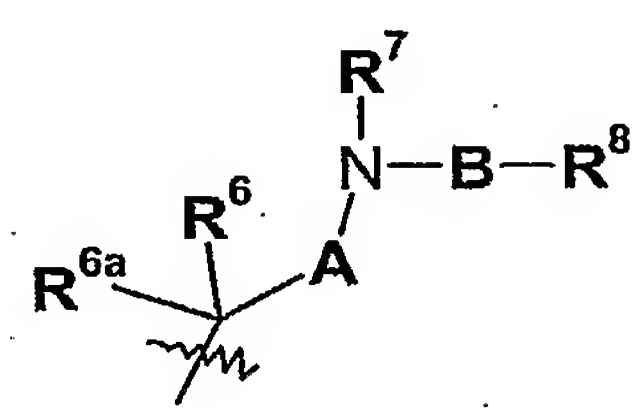
Formula (Ie)

wherein:

$\mathbf{R^3}$ is selected from a group of Formula (IIa) or Formula (IIb):



Formula (IIa)



Formula (IIb)

B is optionally substituted C_{1-6}alkylene, wherein the optional substituents are independently selected from $\mathbf{R^{12}}$;

$\mathbf{R^7}$ is selected from: hydrogen or C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from: C_{3-7}cycloalkyl, aryl or heterocyclyl each of which is optionally substituted by one or substituents independently selected from $\mathbf{R^{12}}$ or $\mathbf{R^{13}}$;

and **A**, **M**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^4}$, $\mathbf{R^5}$ $\mathbf{R^6}$, $\mathbf{R^{6a}}$ and $\mathbf{R^{11}}$ are as defined above for a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

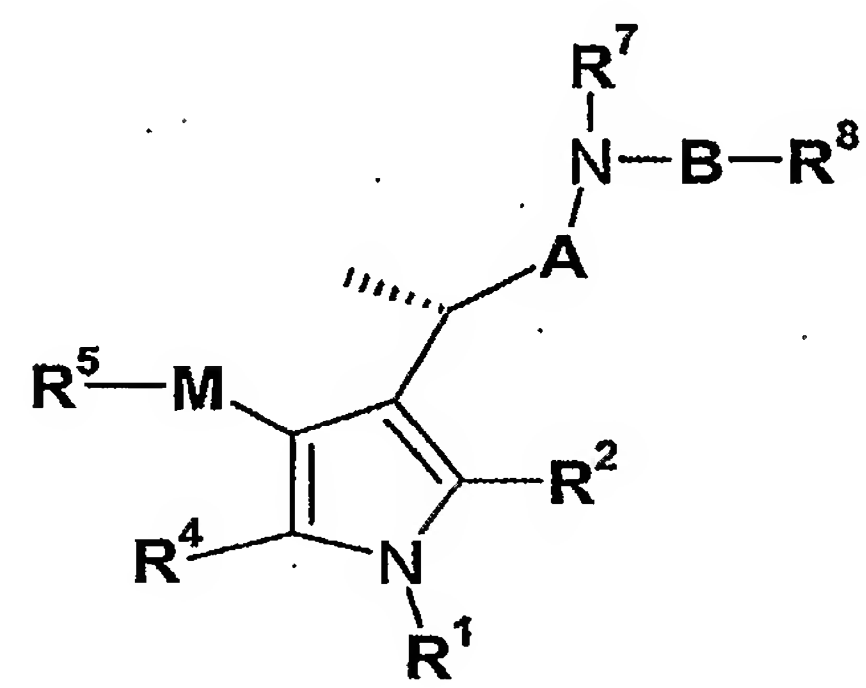
According to a further aspect of the invention there is provided a compound of Formula (Ie)

wherein

$\mathbf{R^8}$ is selected from: aryl optionally substituted by one or substituents independently selected from $\mathbf{R^{12}}$ or $\mathbf{R^{13}}$, preferably substituted $\mathbf{R^{12}}$;

or a salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (If):



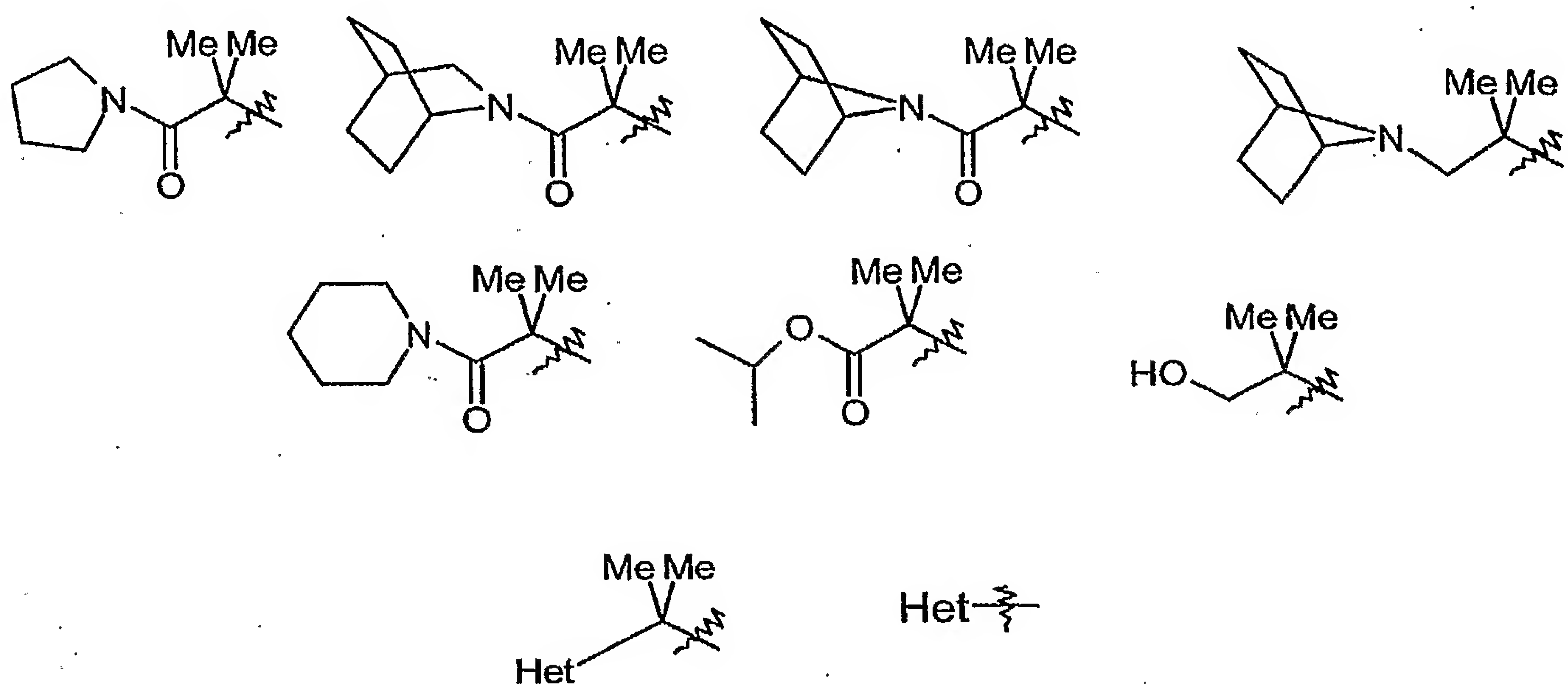
Formula (If)

wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$; $\mathbf{R^7}$, $\mathbf{R^8}$, **A**, **B** and **M** are as defined above

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie) or (If), wherein:

R^5 is selected from one of the following groups:

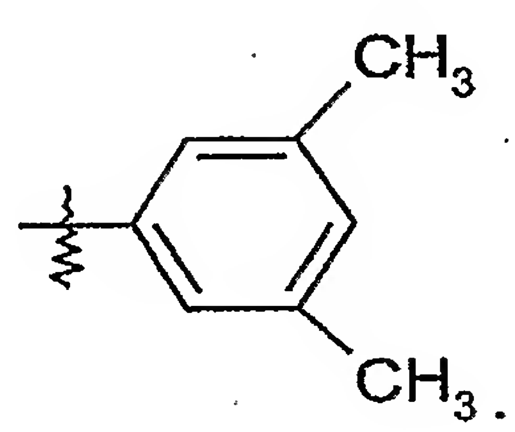


wherein Me represents methyl and het is as defined above.

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie) or (If), wherein:

R^2 represents

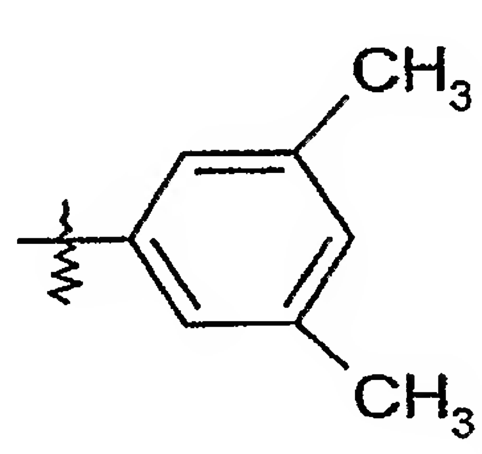


;

or salt, solvate or pro-drug thereof.

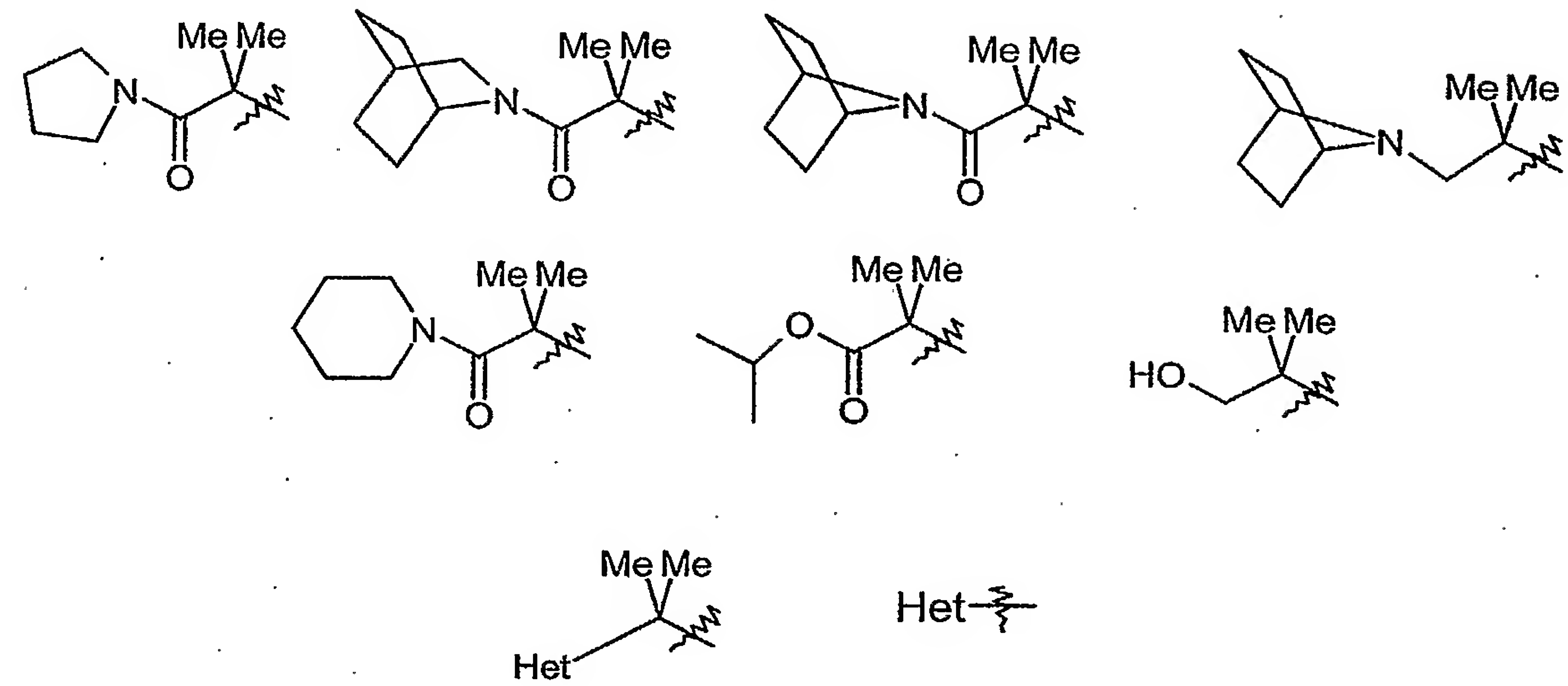
A further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie) or (If), wherein:

R^2 represents



; and

R^5 is selected from one of the following groups:



wherein Me represents methyl and het is as defined above.

or salt, solvate or pro-drug thereof.

Particularly preferred compounds according to the present invention are wherein the compound is selected from:

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(4-hydroxypiperidin-1-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(1,1-dioxo-isothiazolidin-2-ylcarbonyl)-4-methoxy-piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(2-{4-N-isopropylureidophenyl}ethylamino)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

or a salt, pro-drug or solvate thereof.

More particularly preferred compounds according to the present invention are wherein the compound is selected from:

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(4-hydroxypiperidin-1-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(1,1-dioxo-isothiazolidin-2-ylcarbonyl)-4-methoxy-piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(2-{4-N-isopropylureidophenyl}ethylamino)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

or a salt, pro-drug or solvate thereof.

The most preferred compound according to the present invention is:

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(2-{4-N-isopropylureidophenyl}ethylamino)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole;

or a salt, pro-drug or solvate thereof.

The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I). Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable

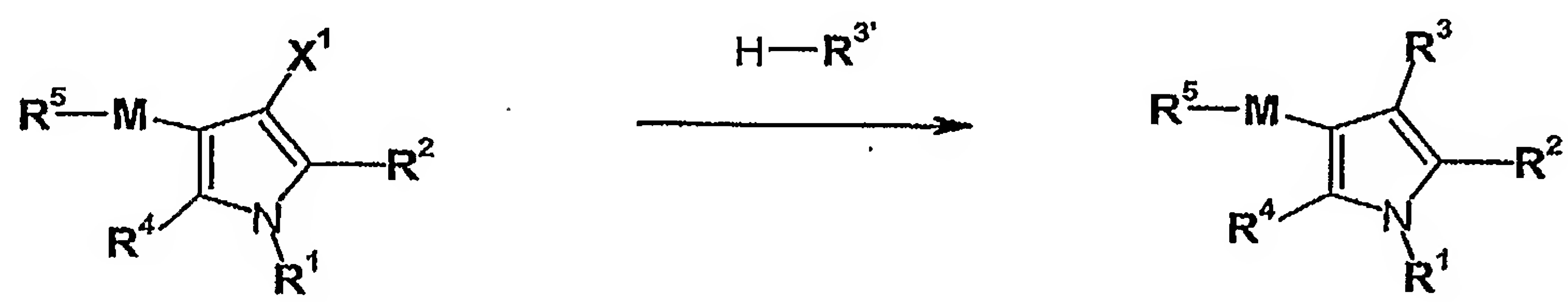
pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

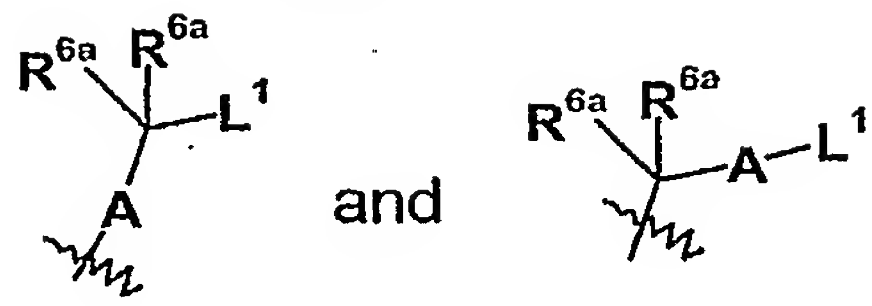
A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

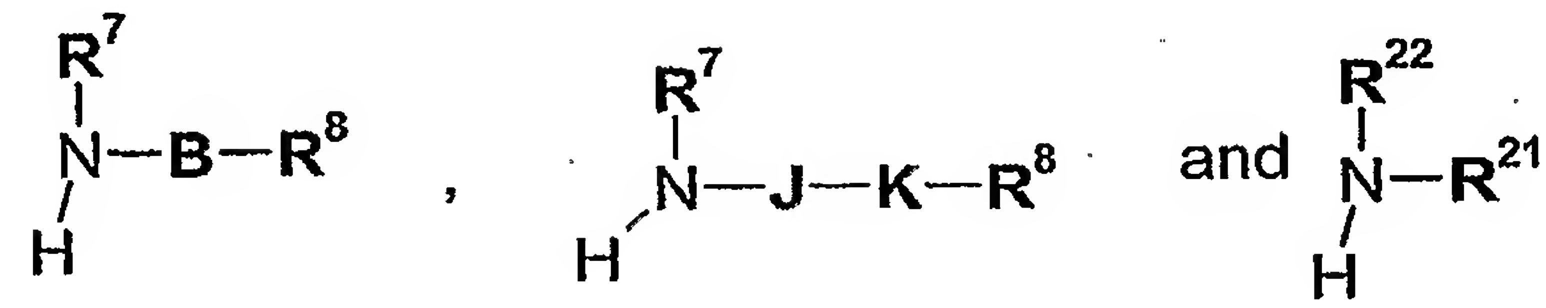
The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (h) as follows, these processes are provided as a further feature of the invention:-

(a) Reaction of a compound of formula **XXXII** with a compound of formula H-$\mathbf{R^{3'}}$ to form a compound of Formula (I),

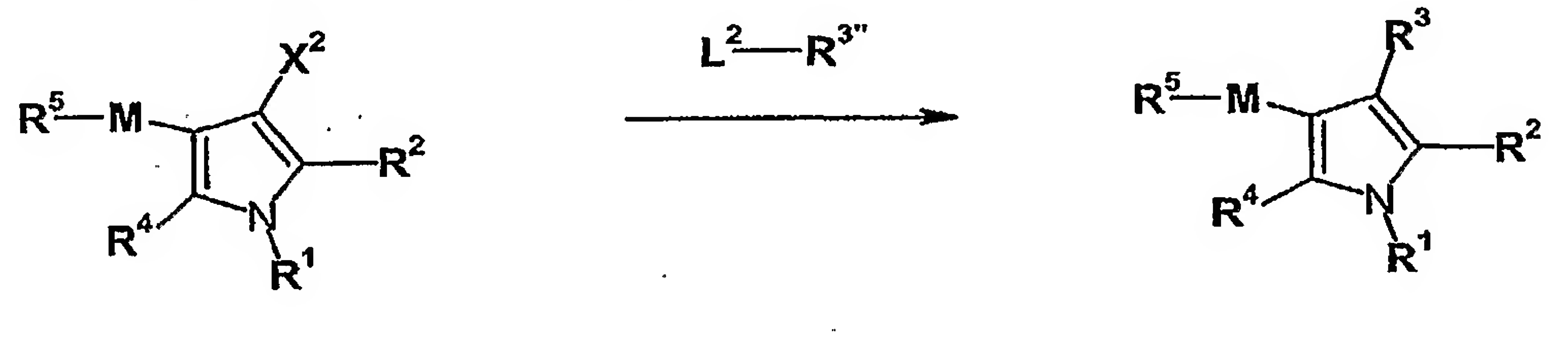


XXXII **Formula (I)**

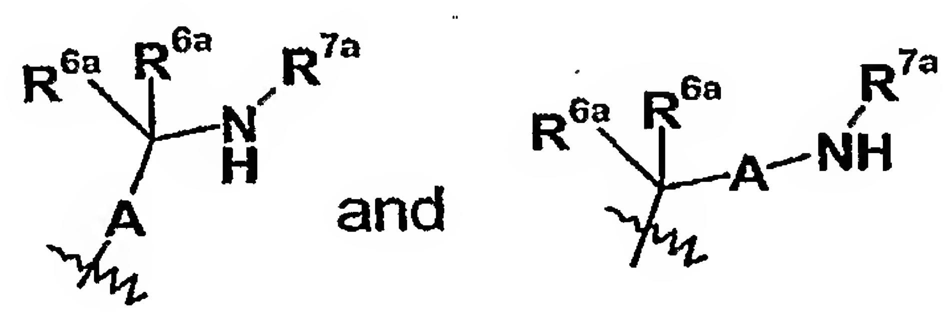
wherein X^1 is selected from:  ; L^1 is a displaceable group; and

$H\text{-}R^{3'}$ is selected from:  ;

(b) Reaction of a compound of formula **XXXIII** with a compound of formula $L^2\text{-}R^{3''}$ to form a compound of Formula (I),



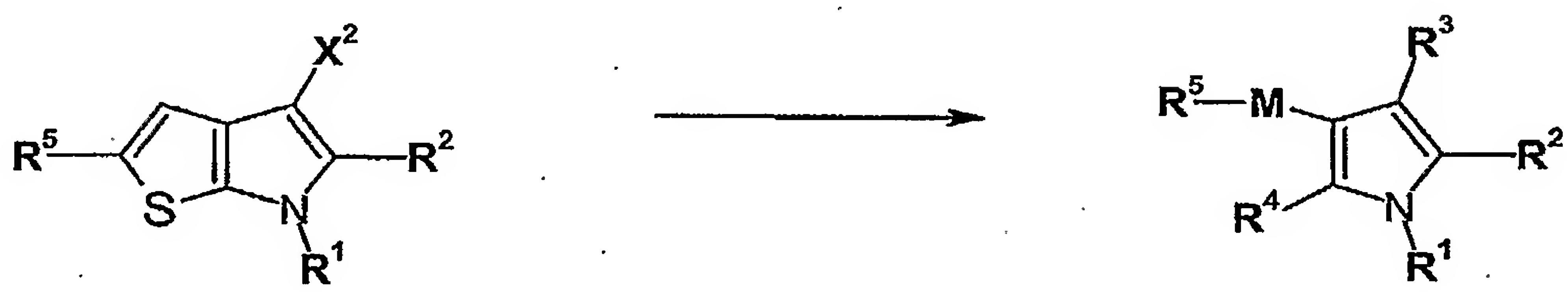
XXXIII **Formula (I)**

wherein X^2 is selected from:  ; L^2 is a displaceable group and R^{7a} is selected from the definition of R^7 or R^{22} above, and

$L^2\text{-}R^{3''}$ is selected from: $L^2{-}B{-}R^8$; $L^2{-}J{-}K{-}R^8$ and $L^2{-}R^{21}$

(c) For compounds of Formula (I) wherein R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId) and R^7 is other than part of a heterocyclic ring or hydrogen, reaction of a compound of Formula (I) wherein R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId) and R^7 is hydrogen with a group of formula $L^3\text{-}R^{7a}$, wherein R^{7a} is as defined above for R^7 with the exclusion of hydrogen and L^3 is a displaceable group;

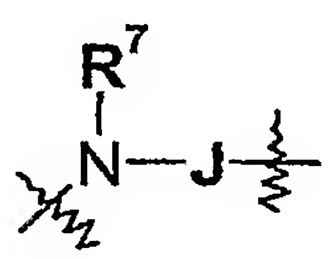
(d) For compounds of Formula (I) wherein $\mathbf{R^4}$ is hydrogen, reduction of a thienopyrrole of Formula XXXVIII to a compound of Formula (I)

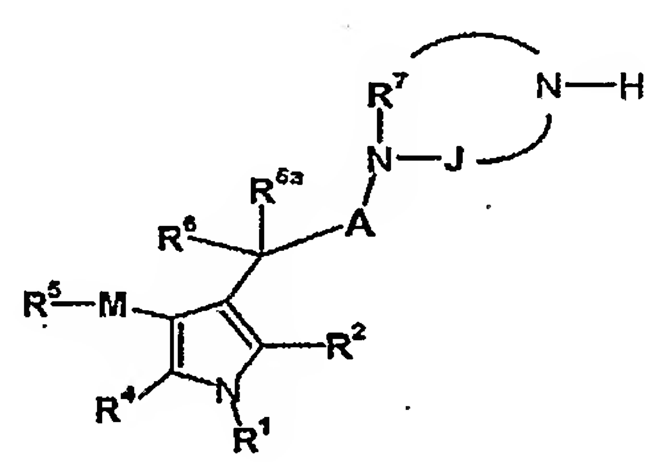


XXXVII

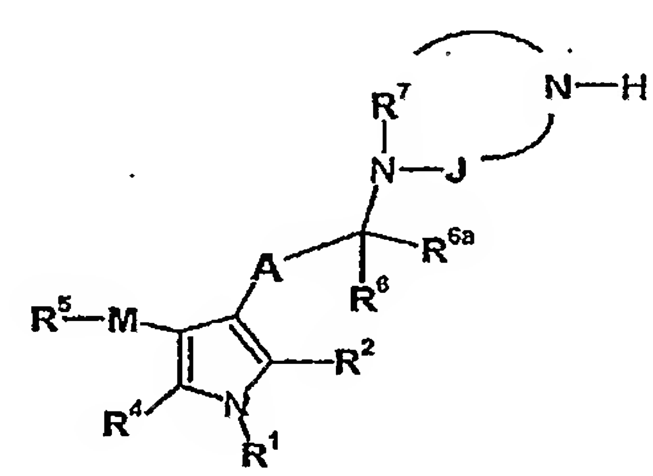
Formula (I)

(e) For compounds of Formula (I) wherein $\mathbf{R^3}$ is a group of Formula (IIe) or (IIf) and $\mathbf{R^{22}}$ is other than hydrogen, reaction of a compound of Formula (I) wherein $\mathbf{R^3}$ is a group of Formula (IIe) or (IIf) and $\mathbf{R^{22}}$ is hydrogen with a group of formula $\mathbf{L^5}$-$\mathbf{R^{22a}}$, wherein $\mathbf{R^{22a}}$ is as defined above for $\mathbf{R^{22}}$ with the exclusion of hydrogen and $\mathbf{L^5}$ is a displaceable group;

(f) For compounds of Formula (I) wherein $\mathbf{R^3}$ is a group of Formula (IIc) or (IId) and the group  together forms an optionally substituted nitrogen-containing heterocyclic ring containing 4-7 carbons atoms, reaction of a compound of Formula **XXXIVa** or **XXXIVb**, with a compound of Formula $\mathbf{L^6}$-**K**-$\mathbf{R^8}$, wherein $\mathbf{L^6}$ is a displaceable group

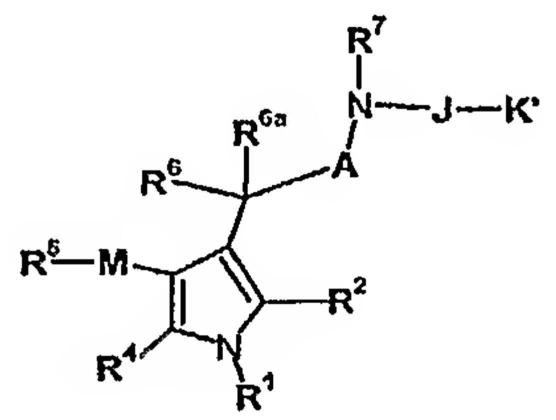


XXXIVa

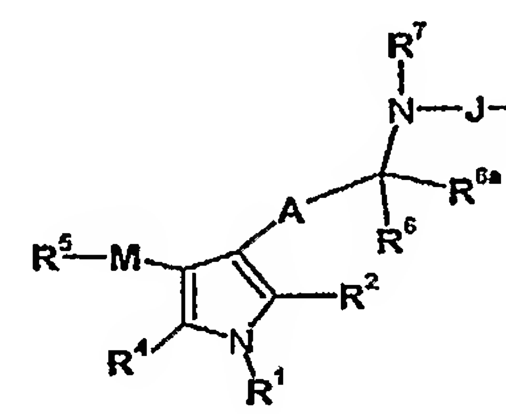


XXXIVb

(g) For compounds of Formula (I) wherein $\mathbf{R^3}$ is a group of Formula (IIc) or (IId), reaction of a compound of Formula **XXXVa** or **XXXVb**, with a compound of Formula $\mathbf{L^7}$-**K''**-$\mathbf{R^8}$, wherein $\mathbf{L^7}$ is a displaceable group, and wherein the groups **K'** and **K''** comprise groups which when reacted together form **K**,

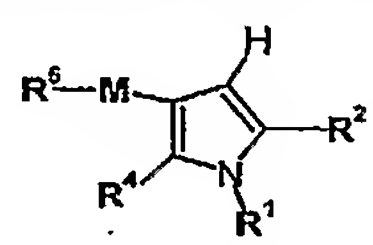


XXXVa



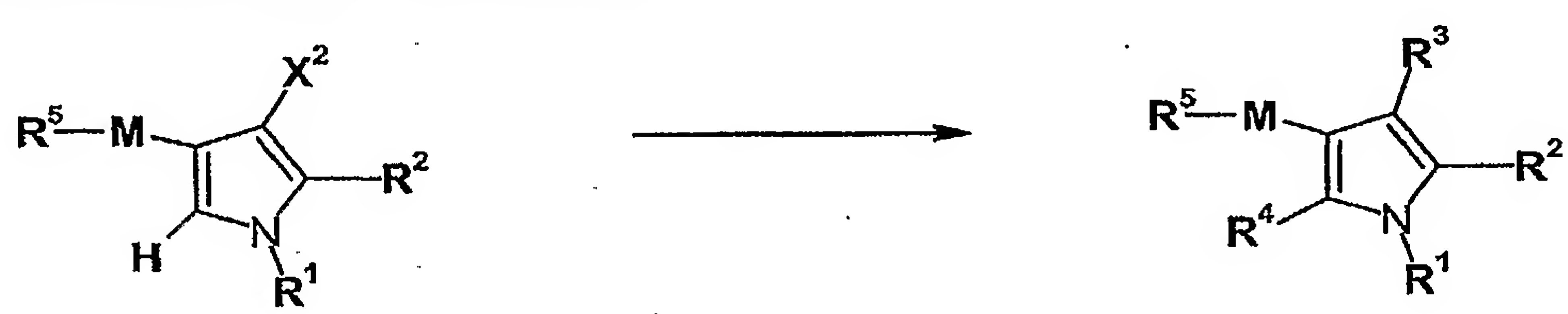
XXXVb ;

(h) reaction of a compound of Formula **XXXVI** with an electrophillic compound of the formula $\mathbf{L^8}$-$\mathbf{R^3}$, wherein $\mathbf{L^8}$ is a displaceable group



XXXVI

(i) reaction of a compound of Formula XXXIX with an appropriate electrophillic reagent to give a compounds of Formula (I)



XXXIX **Formula (I)**

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.

Specific reaction conditions for the above reations are as follows:

Process a) Compounds of formula **XXXII** and H-$\mathbf{R^{5'}}$ can be coupled together in the presence of an organic base (such as DIPEA [di-isopropylethylamine]) or an inorganic base (such as potassium carbonate) base, in a suitable solvent such as DMA or DMF, at a

temperature from room temperature and 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate;

Process b) Compounds of **XXXIII** and $\mathbf{L^2}$-$\mathbf{R^{3''}}$ can be coupled together in the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate,

alternatively if $\mathbf{L^2}$ is a hydroxy group then the $\mathbf{L^2}$-$\mathbf{R^{3''}}$;can be reacted with a compound of formula **XXXIII** under Mitsunobu reaction conditions;

Process c, e and f) Reaction conditions to facilitate these reactions can be using (i) alkylation reaction conditions or (ii) acylation reaction conditions: Examples of said conditions include:

(i) alkylation reaction conditions - the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMF, DMA, DCM, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, methane sulphonate or toluene sulphonate;

(ii) acylation reaction conditions - presence of organic base, such as triethylamine, temperature 0°C to 50-60°C in a suitable solvent such as DCM. Suitable displaceable groups include an acylchloride or an acid anhydride,

Process d) treatment of a compound of Formula XXXVIII with Raney-Nickel under hydrogen in a suitable solvent such as ethanol or methanol at a temperature between room temperature and the boiling point of the solvent.

Process g) The skilled man would be familiar with a variety of reaction conditions and values for **K'** and **K''**, which when reacted together would form the group **K**, examples of said conditions and values for **K'** and **K''** include:

(i.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-N(\mathbf{R}^{17})C(O)-(CH_2)_{s2}-$ these can be prepared by reacting a compound where **K'** is $-(CH_2)_{s1}-N(\mathbf{R}^{17})H$ with a carboxylic acid for formula $HOOC-(CH_2)_{s2}-\mathbf{R}^8$ to form the amide. Coupling of amino groups with carboxylic acids are well known in the art and can be facilitated by a number of chemical reactions using an appropriate coupling reagent. For example a carbodiimide coupling reaction can be performed with EDCl in the presence of DMAP in a suitable solvent such as DCM, chloroform or DMF at room temperature;

(ii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$- C(O)N(R^{17}) -$(CH_2)_{s2}$- these can be prepared by* reacting a compound where **K'** is -$(CH_2)_{s1}$-COOH with an amine of the HN($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-$\mathbf{R}^8$ to form the amide. Methodology is identical to processes described in (i) above in this section;

(iii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$- N(R^{17})C(O)O -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)H with a chloroformate of formula ClC(O)O--$(CH_2)_{s2}$-$\mathbf{R}^8$ in a suitable solvent, such as DCM or chloroform, in the presence of a base, such as *N*-methylmorpholine, pyridine or triethylamine, at a temperature between -10°C and 0°C;

(iv.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$- OC(O)N(R^{17}) -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-OC(O)Cl with a compound of formula HN($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-$\mathbf{R}^8$. Methodology is identical to processes described in (iii) above in this section;

(v.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-N(R^{17})*S(O_2)*-$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)H with a sulphonyl chloride of formula ClS(O_2)-$(CH_2)_{s2}$-$\mathbf{R}^8$ in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and room temperature;

(vi.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-*S(O_2)*N(R^{17}) -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-S(O_2)Cl with a compound of HN($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-$\mathbf{R}^8$. Methodology is identical to processes described in (v) above in this section

(vii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$- N(R^{17}) -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-$\mathbf{L}^{11}$ with a compound of formula HN($\mathbf{R}^{17}$)-$(CH_2)_{s2}$-$\mathbf{R}^8$, wherein $\mathbf{L}^{11}$ is a displaceable group. This reaction can be performed in the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein **K'** is -$(CH_2)_{s1}$-N($\mathbf{R}^{17}$)H with a compound of formula $\mathbf{L}^{11}$-$(CH_2)_{s2}$-$\mathbf{R}^8$, under identical conditions.

(viii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-O -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-OH with a compound of formula **L^{12}**-$(CH_2)_{s2}$-**R^8**, wherein **L^{12}** is a displaceable group. This reaction can be performed in the presence of an organic base (such as potassium *t*-butoxide) or an inorganic base (such as sodium hydride), in a suitable solvent such as DMA or DMF, at a temperature from room temperature and 120°C. Suitable displaceable groups include: a halide, such as bromo, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein **K'** is -$(CH_2)_{s1}$-**L^{12}** with a compound of formula HO-$(CH_2)_{s2}$-**R^8**, under identical conditions.

(ix.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-C(O) -$(CH_2)_{s2}$-* these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-C(O)-**L^{13}** with a Grignard reagent of formula BrMg$(CH_2)_{s2}$-**R^8**, wherein **L^{13}** is a displaceable group. This reaction can be performed in a non-polar solvent such as THF or diethylether at a temperature between room temperature and the boiling point of the solvent. Suitable displaceable groups include: a halide, such as bromo, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein **K'** is -$(CH_2)_{s1}$-MgBr with a compound of formula **L^{13}**-C(O)-$(CH_2)_{s2}$-**R^8**, under identical conditions.

Process h) reaction of a compound of Formula **XXXVI** with a compound of the formula **L^8-R^3** , can be performed under Friedel Craft conditions, for example in the presence of diethylaluminium chloride in a suitable solvent, such as DCM, in an inert atmosphere such as nitrogen, at a temperature between room temperature and the boiling point of the solvent or under Mannich conditions, for example, formaldehyde and a primary or secondary amine in acetic acid, in an inert atmosphere such as nitrogen at a temperature between room temperature and 100°C.

Process i) reaction of a compound of Formula **XXXIX** with an appropriate electrophilic reagent can be used to add an R^4 group. For example, when R^4 is a halogen, such as chlorine, an electrophilic reagent such as N-chlorosuccinimide in a suitable solvent, such as THF, at a temperature between room temperature and the boiling point of the solvent can be used, or when R^4 is alkyl, such as ethyl, an electrophilic reagent such as an appropriate alkyl halide, such as ethyl iodide, can be used under Friedel Craft conditions, for example in the presence of diethylaluminium chloride in a suitable solvent, such as CH_2Cl_2, in an inert atmosphere

such as nitrogen, at a temperature between room temperature and the boiling point of the solvent.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

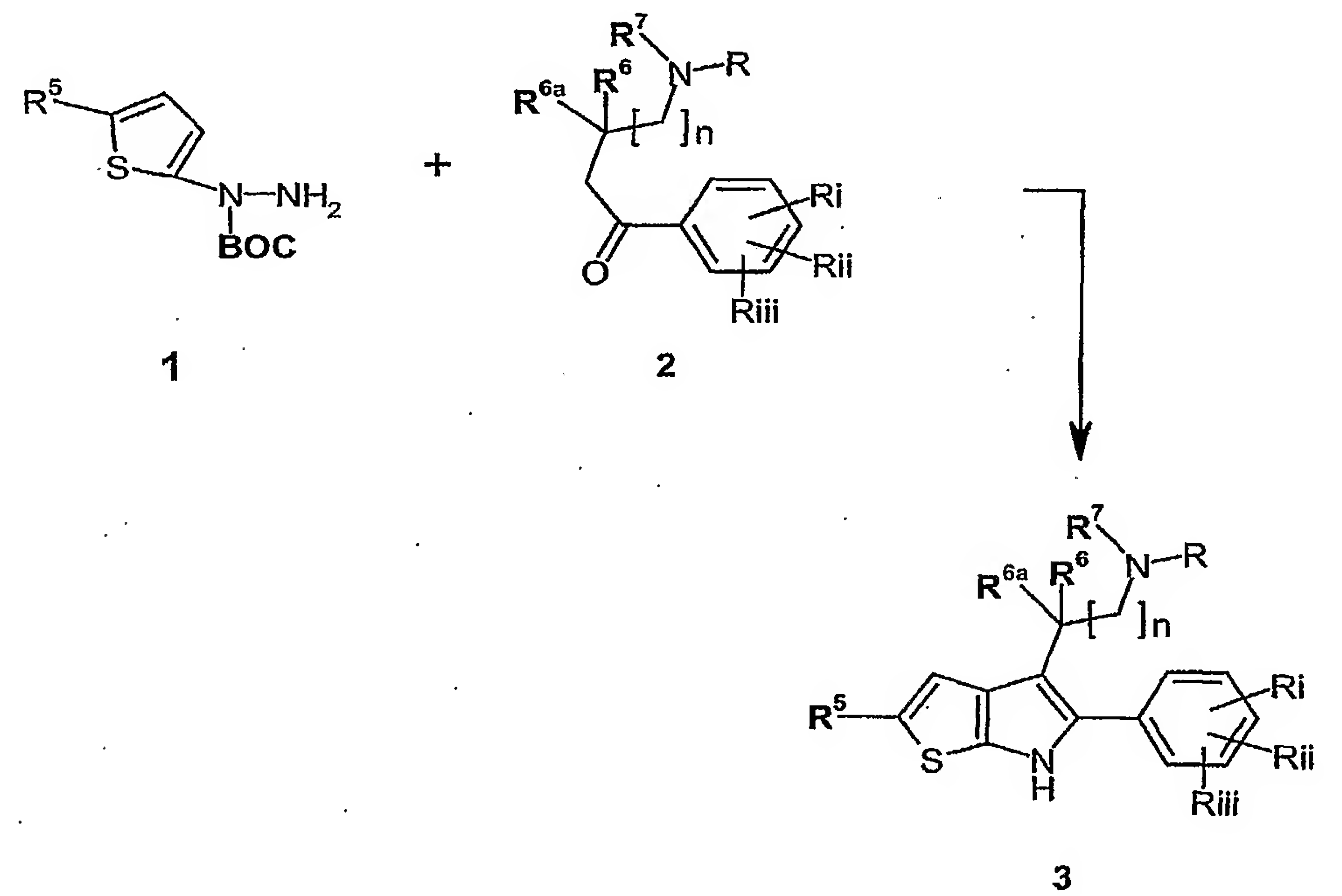
Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

EXPERIMENTAL

GENERAL REACTION SCHEMES

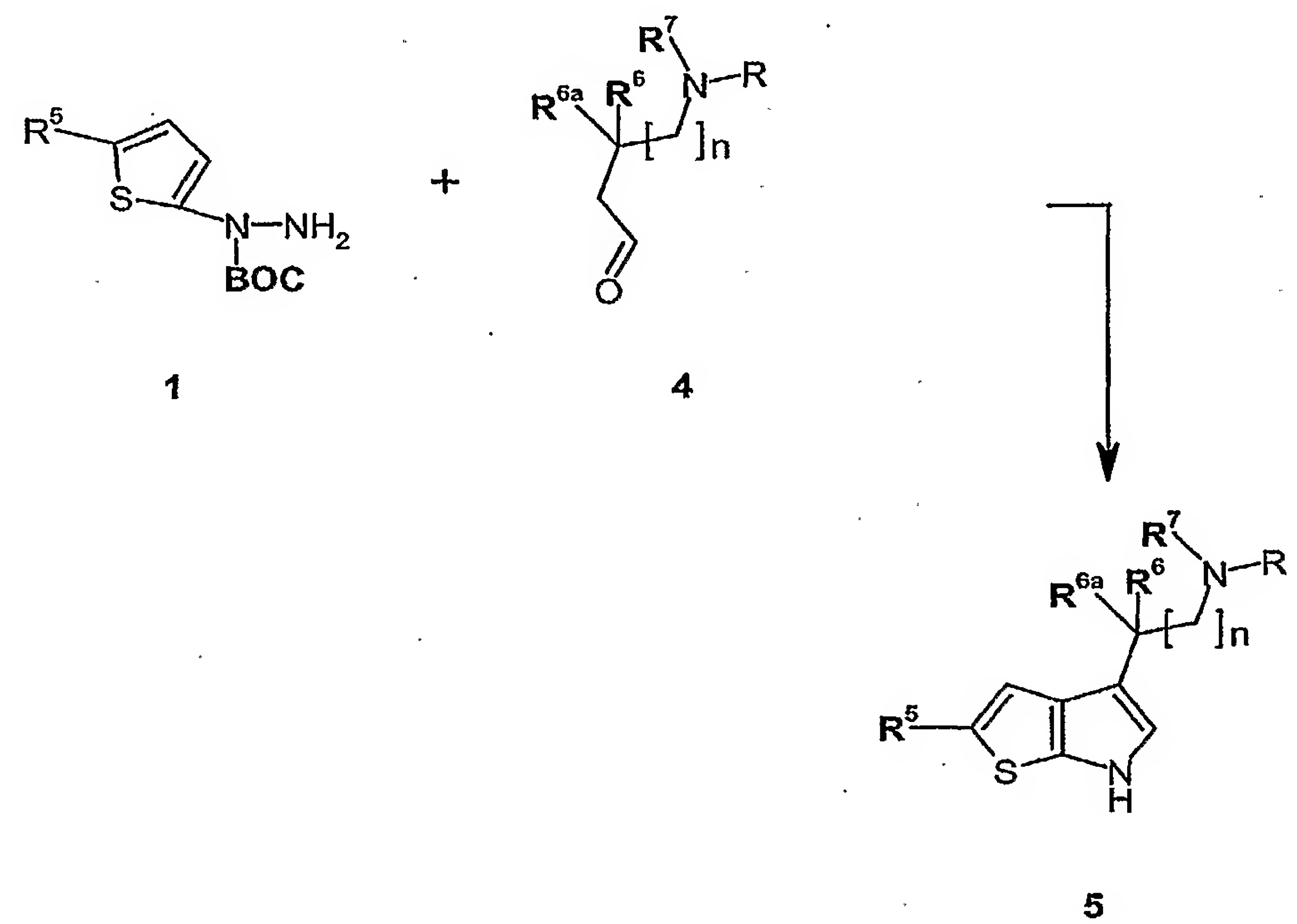
In the following schemes wherein Ri, Rii and Riii represent optional substituents on the phenyl ring which are optionally protected as necessary and R represents a protecting group, group **C** has been depicted as substituted phenyl for illustration purposes only. Other definitions of **C** are also appropriate.



Scheme a

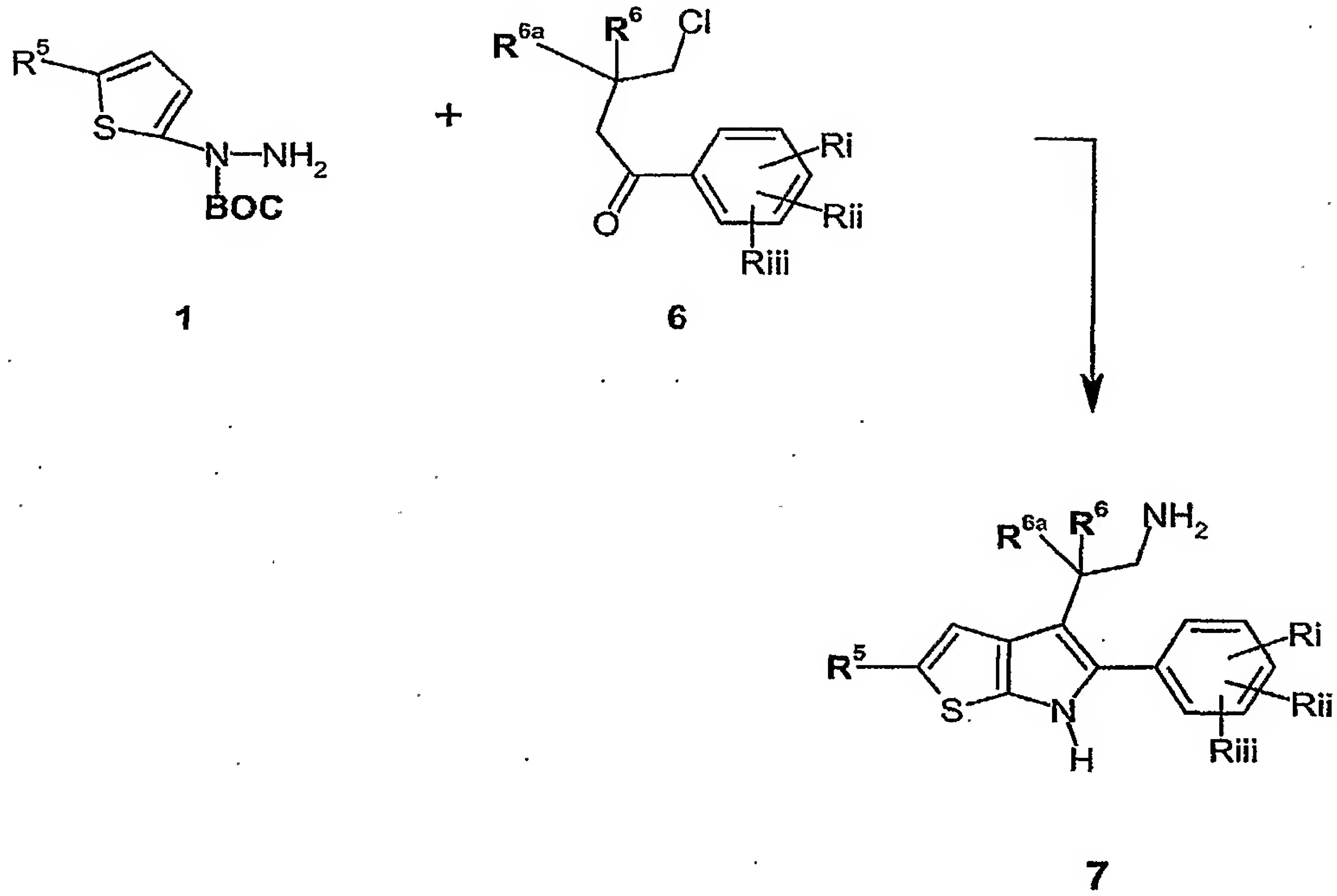
Thienopyrroles, such as **3** can be synthesised by the classic Fisher thienopyrrole synthesis reaction by the condensation of a hydrazine-HCl **1** and a ketone **2**, bearing hydrogen atoms α to the carbonyl (Scheme a). Treatment of these reactants in a suitable solvent, such as

acetic acid, ethanol, *sec*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. R represents a protecting group, eg *tert*-butylcarbamate or phthalimide.



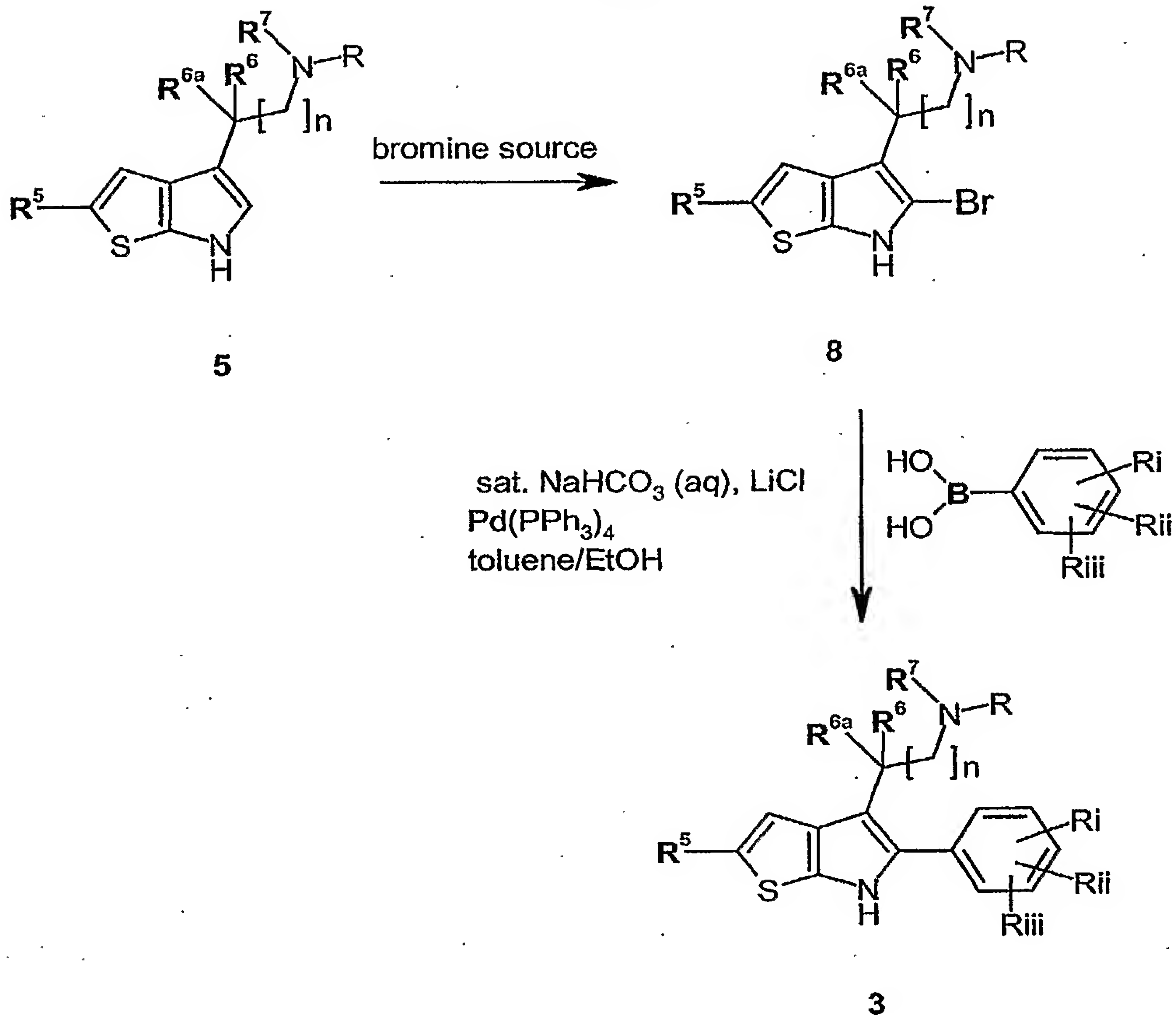
Scheme b

Thienopyrroles, such as represented in structure **5**, can also be made using aldehydes **4**, bearing hydrogen atoms α to the carbonyl, by cyclization using the conditions above. In this case the substituent at the 2-position must be added later (see scheme d).



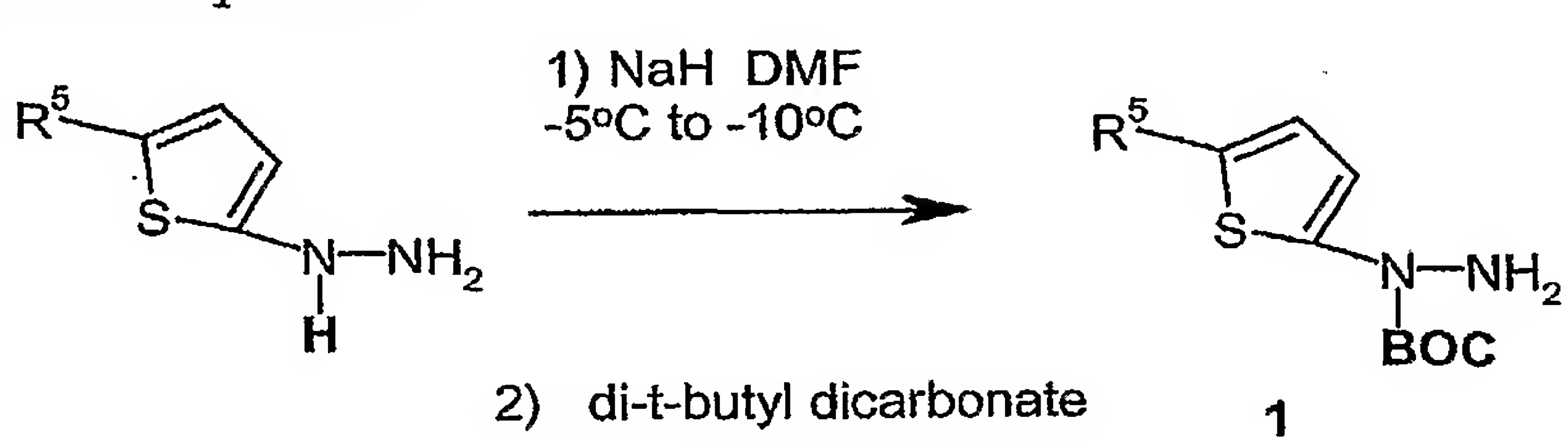
Scheme c

Thienopyrrole may also be synthesised utilising the Granburg reaction, wherein a hydrazine **1** is mixed with ketone **6**, bearing a chlorine atom γ to the carbonyl, and heated in a suitable solvent such as ethanol, *sec*-butanol, toluene at a temperature between 50 °C and 120 °C (Scheme c).

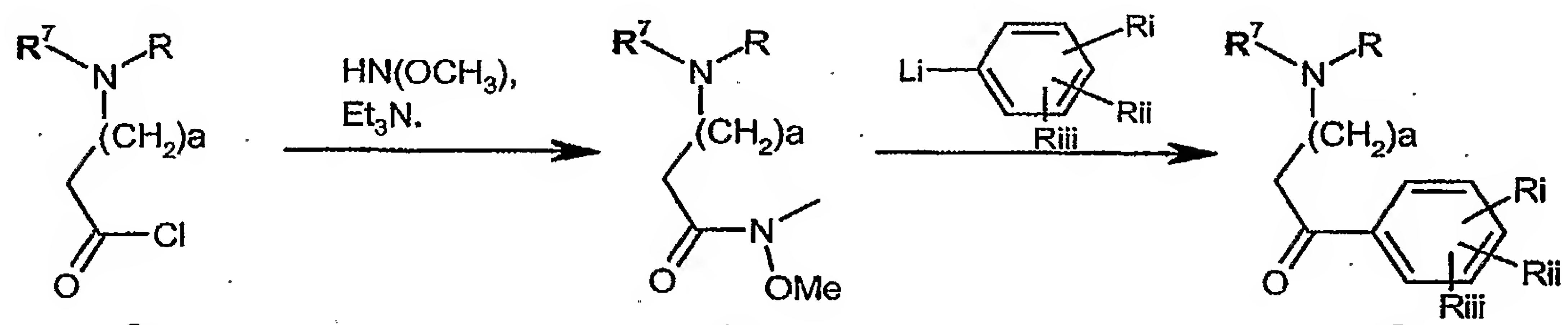


Scheme d

The thienopyrrole **5** can be treated with a 'bromine source', such as molecular bromide, pyridinium tribromide, pyrrolidone hydrobromide or polymer supported reagent equivalents, in an inert solvent such as chloroform, methylene chloride at -10 °C to 25 °C to yield the 2-bromo compound **8** (Scheme d). Reaction under Suzuki conditions with a palladium(0) catalyst, a weak base such as aqueous sodium carbonate or saturated sodium hydrogen carbonate and the like, and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the desired compound **3**.



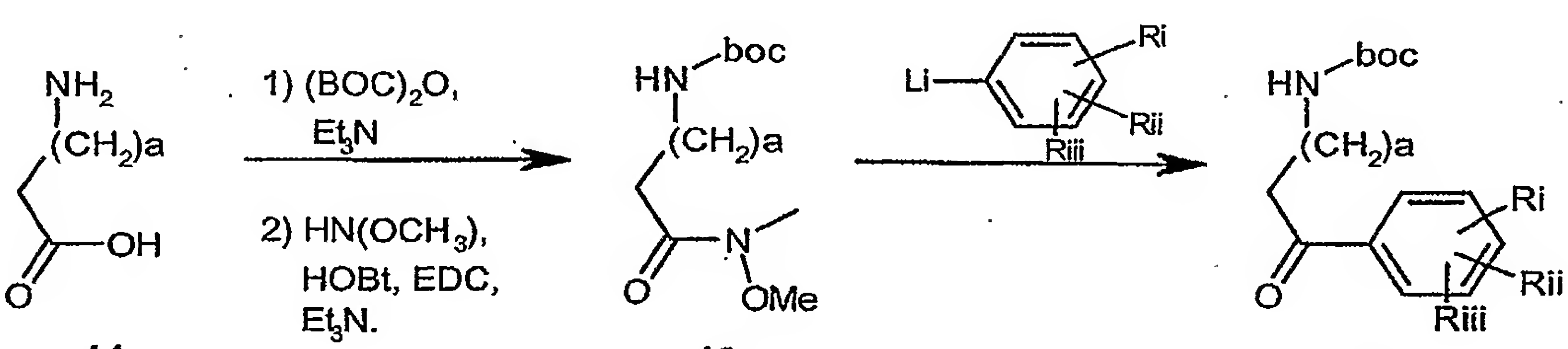
The thiophene **1** can be synthesised by reaction of a hydrazine under the preferred conditions of sodium hydride in DMF at a temperature between -10 °C and -5 °C, followed by reaction with di-tert-butyldicarbonate in THF under reflux.



9 **10** **2**

Scheme e.

Substituted ketones **2** can be prepared, as outlined in Scheme e starting from appropriate acid chlorides such as **9**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine hydrochloride in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **10**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, **1988**, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **2**.

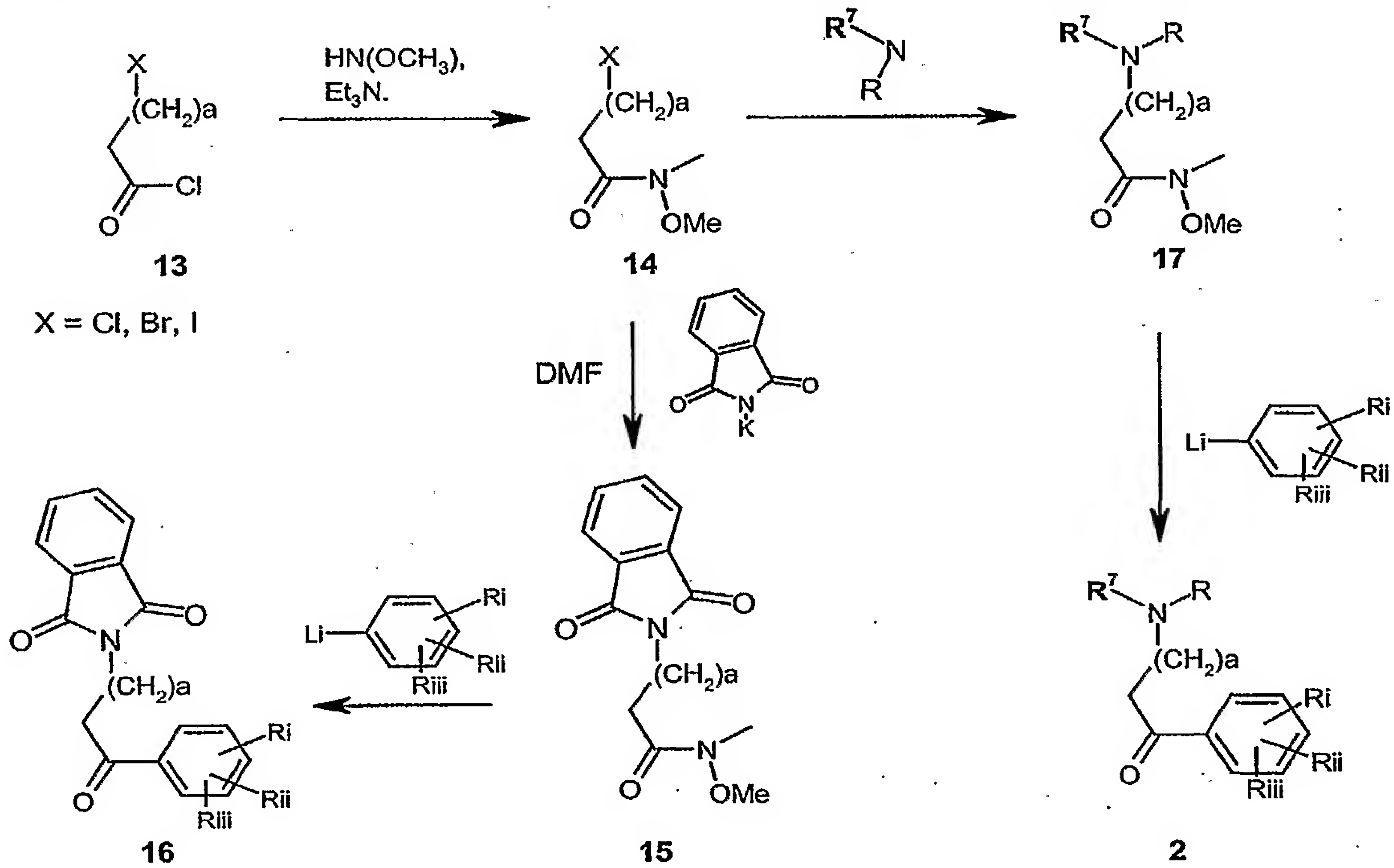


11 **12** **2**

Scheme f.

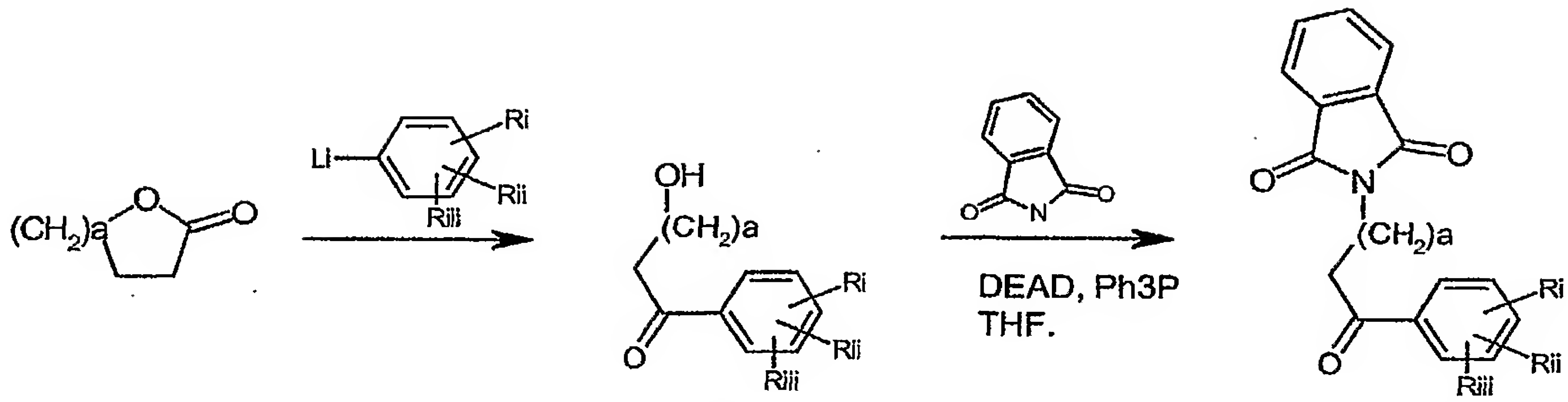
Commencing with a readily available amino acid with a suitable chain length [a] **11**, the nitrogen atom can be brought in at the beginning of the synthesis by the route shown in Scheme f. Protection of the amine group of **11** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl di-carbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C. Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling

reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenzotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 hours provided the corresponding coupled product **12**. Following the same route described above for scheme e, the aryl group can then be installed.



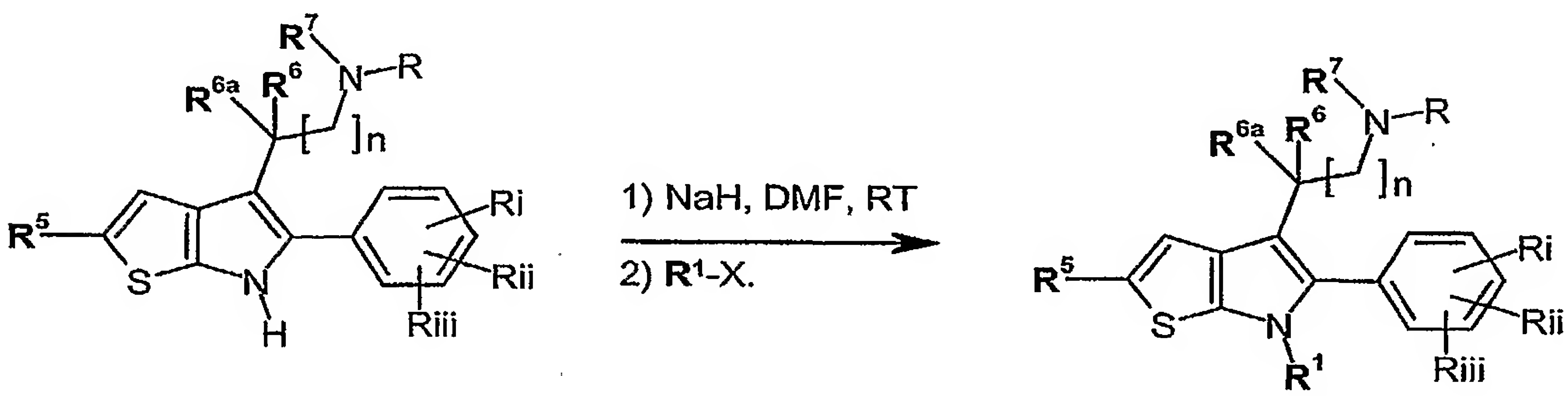
Scheme g.

Scheme g illustrates another method for the synthesis of ketone such as **2** and **16**, where the nitrogen group is introduced at a latter stage. As above a Weinreb amide **14** can be synthesised from an acid chloride. Treatment with the required amine, in an inert solvent such as THF, toluene, water and the such like can displace the group X to give **17**. As above the aryl group can be introduced by displacement of the Weinreb amide with a suitable aryl lithium nucleophile. Alternatively the nitrogen atom can be introduced already protected as a phthalimide by displacement of the group X by potassium phthalimide, or similar salt thereof, by heating in an inert polar solvent such as DMF, DMSO, THF, toluene with or without the presence of a catalyst such as tetrabutylammonium iodide and the such like, to yield the compound **15**. Again displacement of the Weinreb amide with an organolithium species completes the synthesis of ketone 16 suitable for cyclization under the Fischer condition described above for thienopyrrole synthesis.

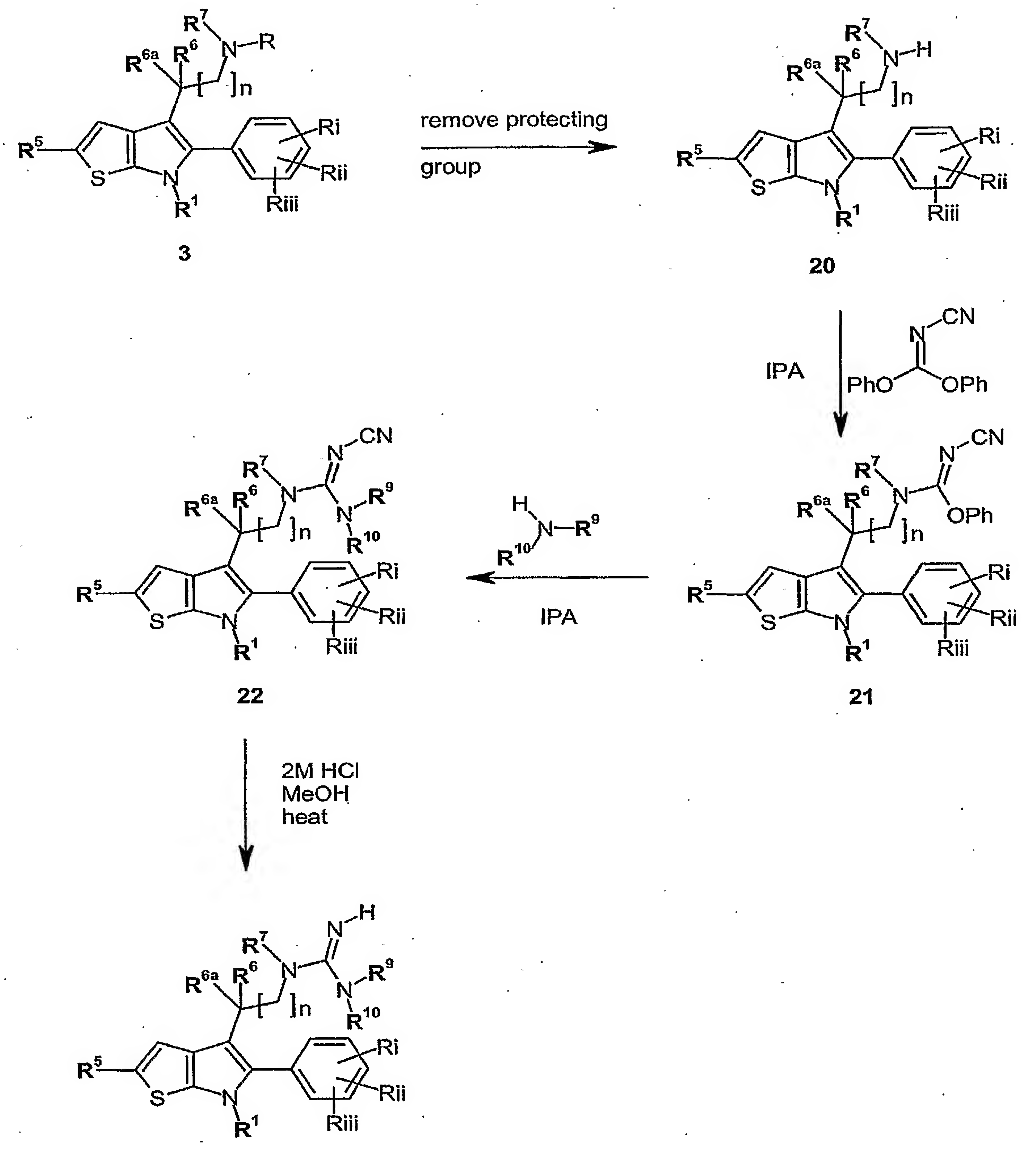


Scheme h.

An alternative approach to a phthalimide protected nitrogen ketone, such as **16**, can be taken by firstly treating a lactone, with an organolithium species as in the above schemes in a suitable solvent such as THF or ether at a low temperature of between –100 °C and –50 °C to yield a primary alcohol **18** (Scheme h). The hydroxyl function of **18** is replaced with a phthalimide group by a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the desired ketone **16**.



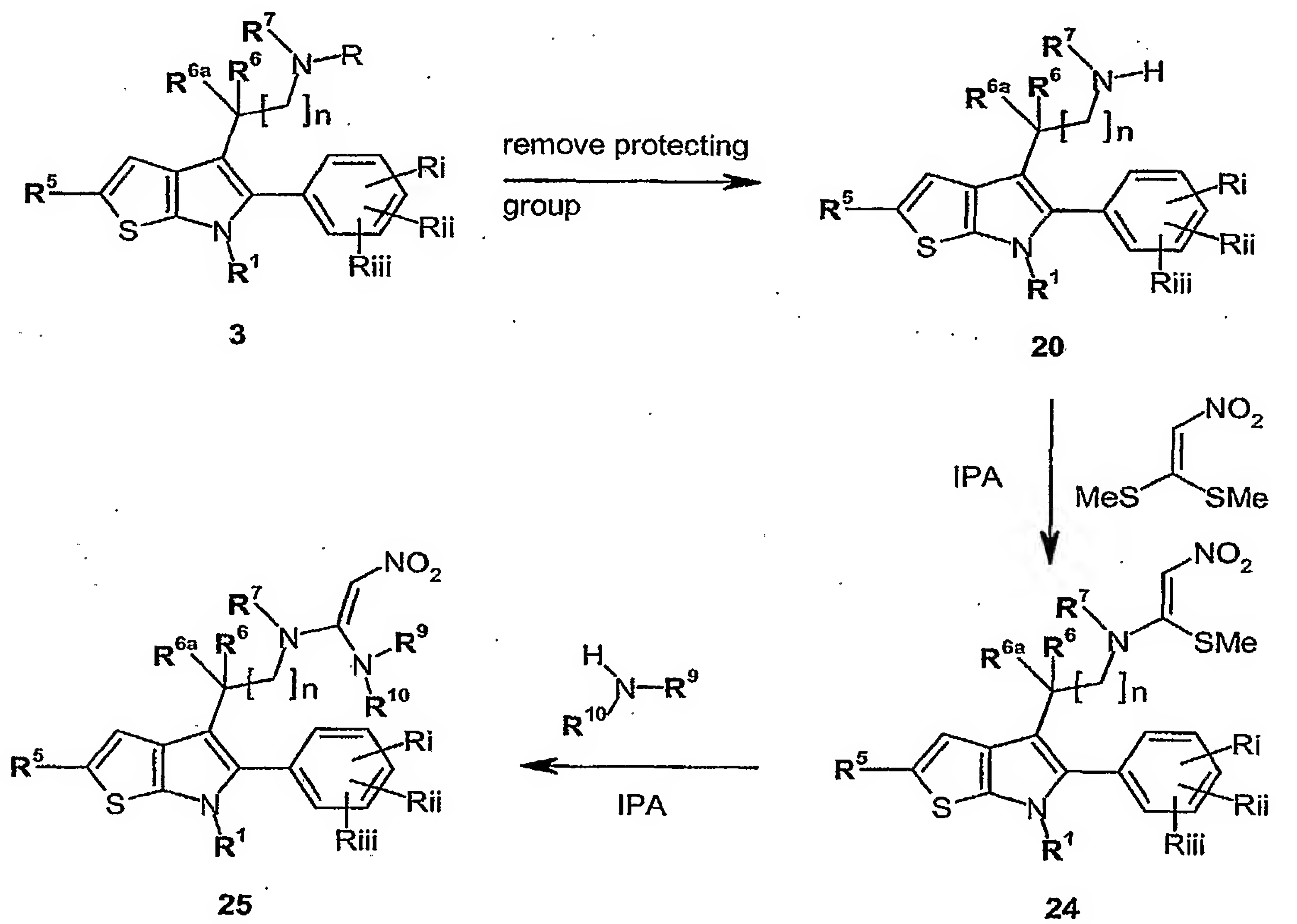
If the group $\mathbf{R^1}$ was not present on the starting hydrazine before cyclization to form a thienopyrrole it may be added post cyclization by an alkylation reaction (**19→3**). The thienopyrrole is de-protonated by a strong base, such as sodium hydride, *n*-butyl lithium, lithium diisopropylamine, sodium hydroxide, potassium *tert*-butoxide in a suitable inert solvent such as THF, DMF, DMSO and the such like, and an alkyl halide added and the mixture stirred at room temperature.



Scheme i

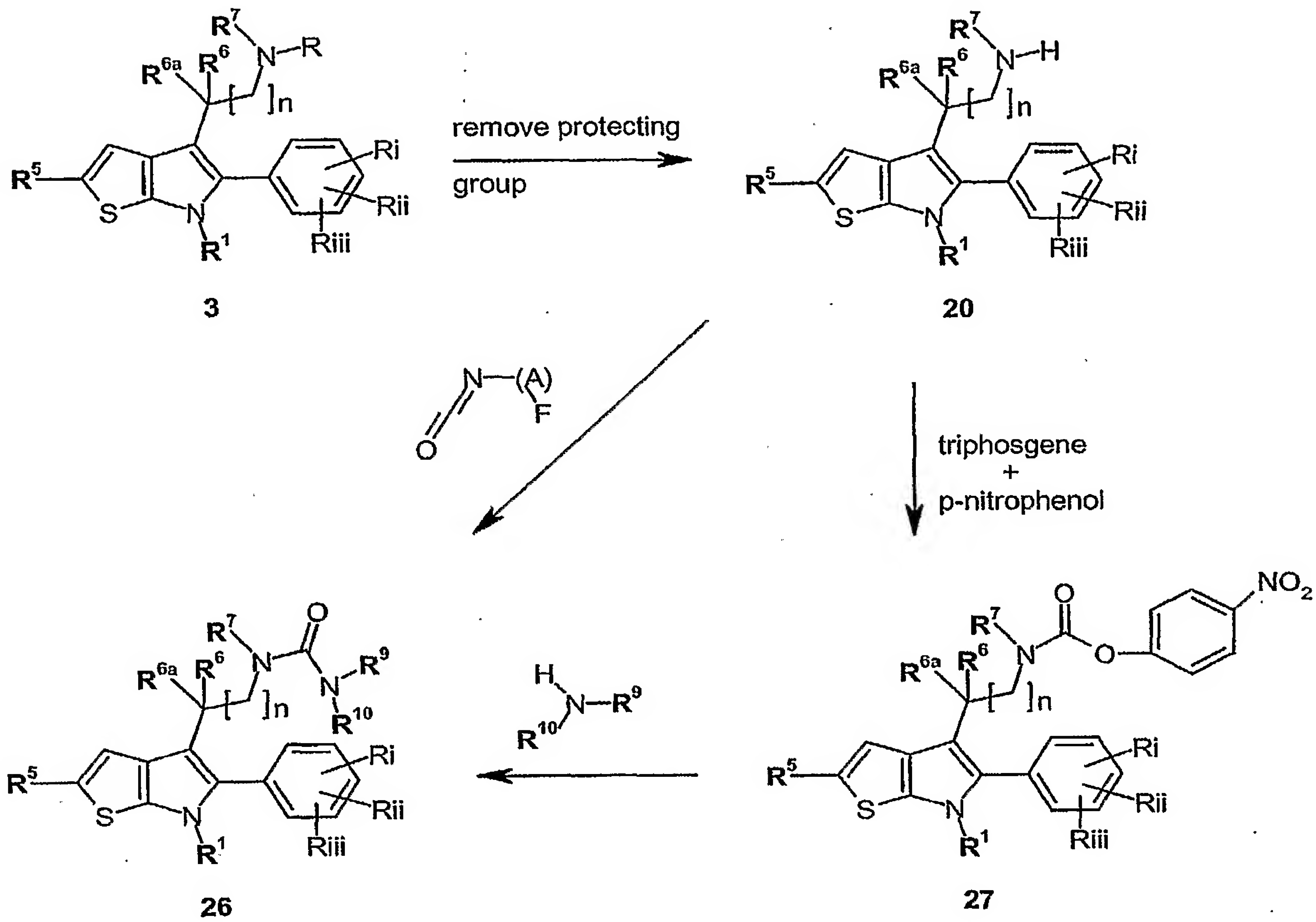
Depending on the route used above a thienopyrrole **20** suitable for conversion to a cyano-guanidine can be formed by removal of the protecting group, for example if a *tert*-butylcarbamate group was used then removal is accomplished using a strong acid, for example trifluoroacetic acid or hydrochloric acid in an inert solvent such as methylene chloride, chloroform, THF or dioxane at a temperature between –20 °C and 25 °C. A

phthalimide group, for example, can be removed by hydrazine in a suitable solvent for example methanol, ethanol, methylene chloride, chloroform, THF dioxane at a temperature between –20 °C and 25 °C. The primary amine **20** can be converted to a cyano-guanidine **22** by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as *iso*-propyl alcohol, methylene chloride, chloroform, benzene, tetrahydrofuran and the like, at a temperature between –20 °C and 50 °C, followed by condensation with an appropriately substituted amine in an inert organic from the list above, with heating at a temperature between –20 °C and 100 °C (Scheme i **20→21→22**). Further treatment of **22** with 2 molar Hydrochloric acid in methanol at elevated temperature yields guanidine compounds **23**.



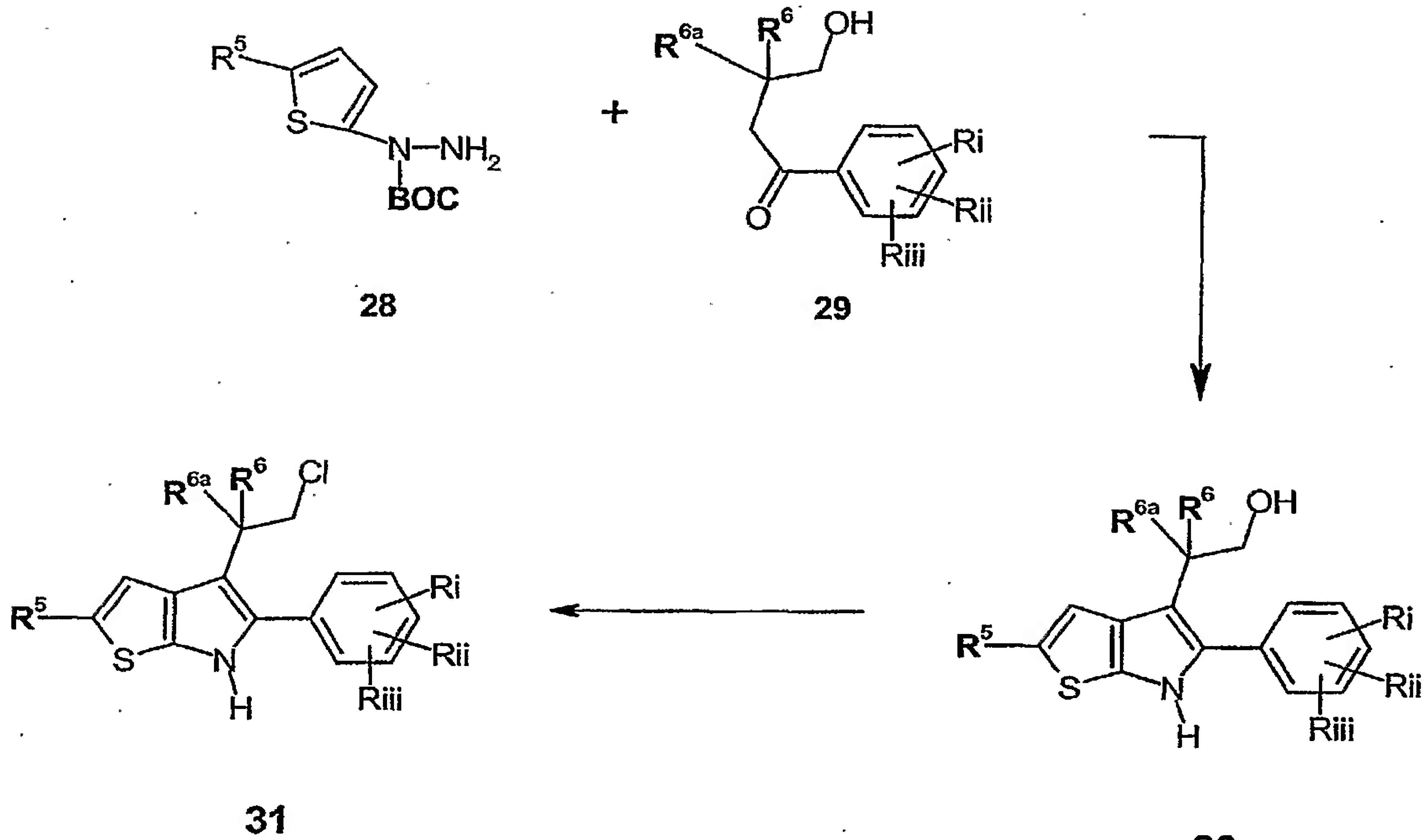
Scheme j.

Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25** (Scheme j, **20→24→25**).



Scheme k.

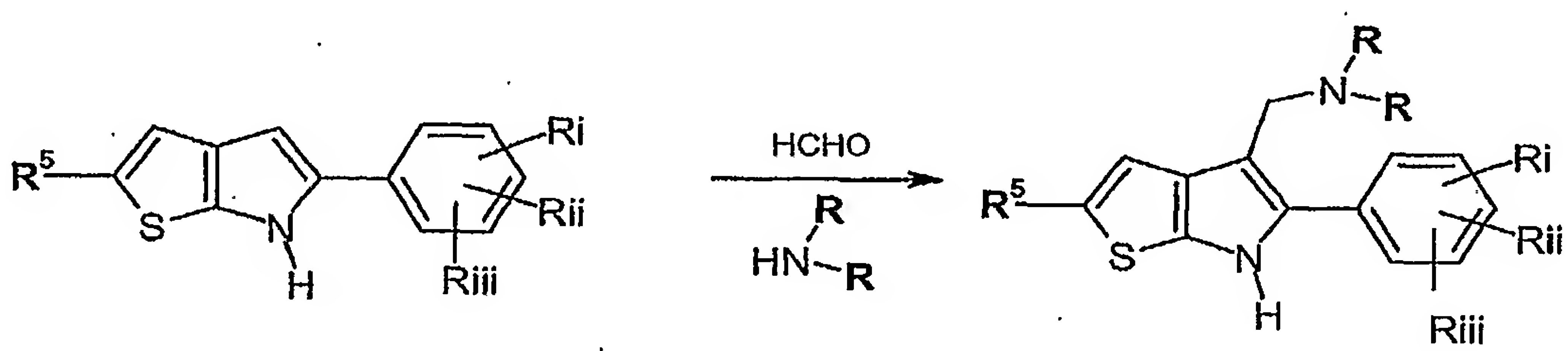
Again in a similar fashion the suitable thienopyrrole **20**, derived from de-protection, can be converted to a urea by either direct treatment with an iso-cyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**20**→**27**) followed by addition of an amine (**27**→**26**), bearing the required substitution to yield **26**.



28 29 30 31

Scheme l.

Chloro thieno-pyrrole intermediates, such as **31**, can be made as shown in Scheme l. **30** can synthesized by the classic Fisher thieno-pyrrole synthesis reaction by the condensation of a hydrazine-HCl **28** and a ketone **29**, bearing hydrogen atoms α to the carbonyl. Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *sec*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. The chloro intermediate **31** can then be synthesized from **30** using, for example, either (i) sulphonyl chloride in methylene chloride at a temperature of about 0°C, or (ii) CCl_4 followed by triphenylphosphine in a solvent such as acetonitrile at a temperature of about 0°C. Thienopyrroles of the invention can then be prepared by displacement of chlorine atom using an appropriate side chain intermediate such as a substituted heterocyclic ring.

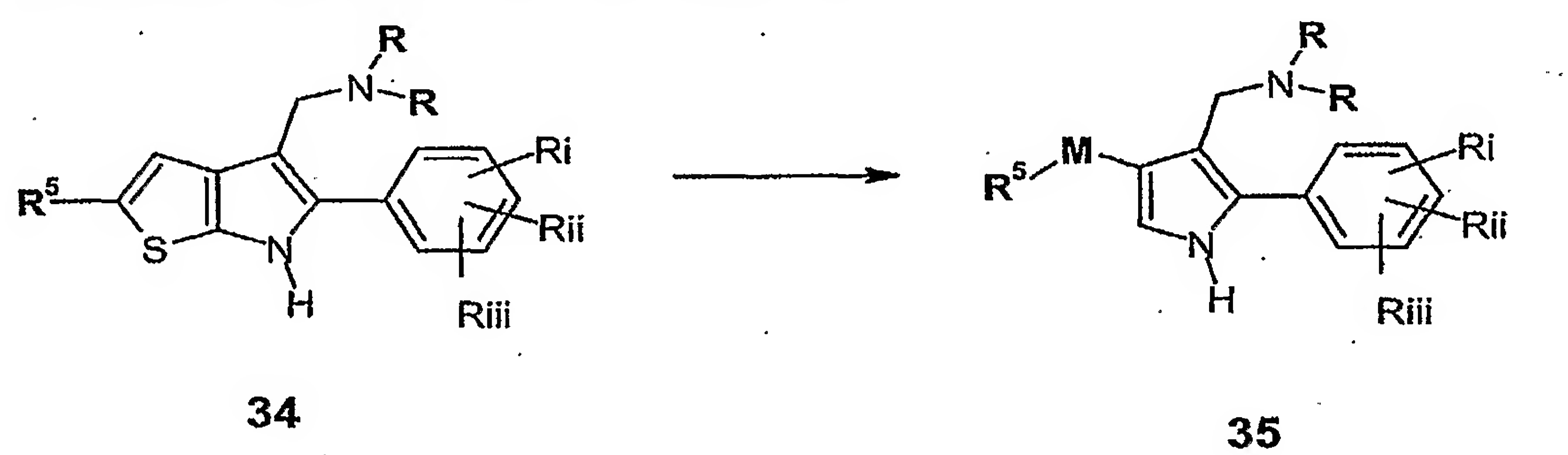


32 34

Scheme m.

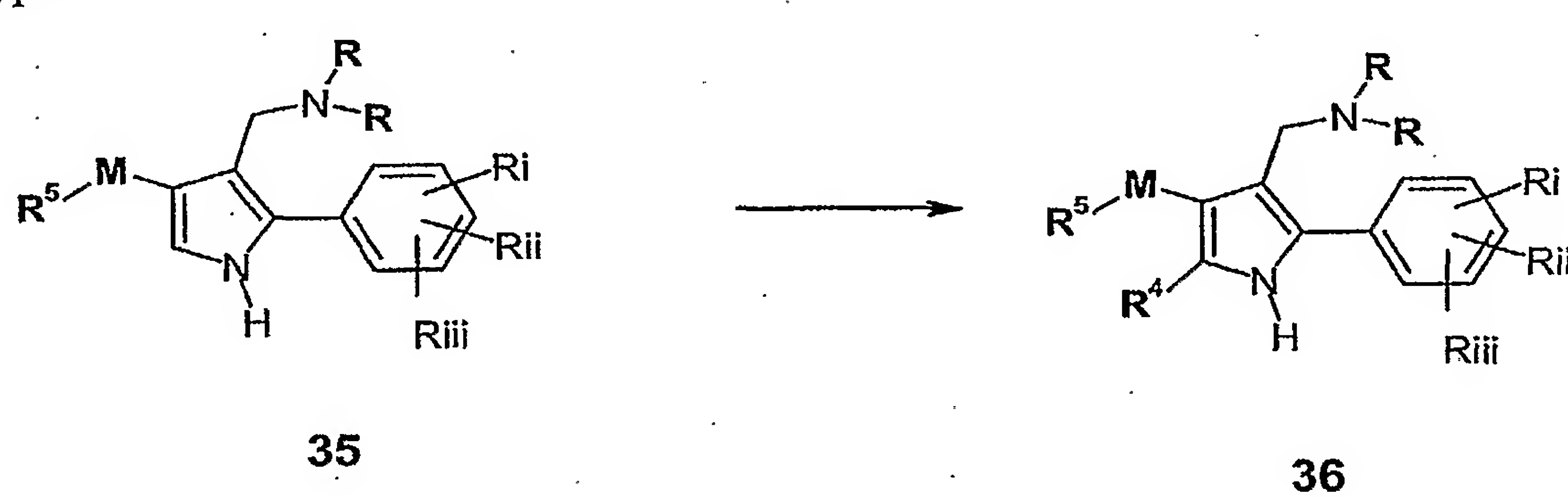
Thienopyrroles of Formula (I) wherein **A** is a direct bond and $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are both hydrogen can be prepared as shown in Scheme m. A thieno-pyrrole **32** can be reacted with formaldehyde and an amine, in a suitable solvent such as acetic acid/dioxan at a temperature of about 0°C to 25°C for between about 1 to 8 hours, to form the thieno-pyrrole **34**.

Thienopyrroles such as **3**, **7**, **23**, **25**, **26** and **34** can then be used to prepare the corresponding pyrrole by reduction, for example, as shown in Scheme n for the conversion of the thienopyrrole **34** to the pyrrole **35**. Reduction conditions such as with Raney-Nickel under hydrogen in a suitable solvent, such as ethanol or methanol, at a temperature between room temperature and the boiling point of the solvent can be used.



Scheme n.

A pyrrole, such as **35**, can be substituted at the 5-position with an R^4 group using an appropriate electrophillic reagent reaction, as shown in Scheme o. For example, when R^4 is a halogen, such as chlorine, an electrophilic reagent such as N-chlorosuccinimide in a suitable solvent, such as THF, at a temperature between room temperature and the boiling point of the solvent can be used, or when R^4 is alkyl, such as ethyl, an electrophilic reagent such as an appropriate alkyl halide, such as ethyl iodide, can be used under Friedel Craft conditions, for example in the presence of diethylaluminium chloride in a suitable solvent, such as CH_2Cl_2, in an inert atmosphere such as nitrogen, at a temperature between room temperature and the boiling point of the solvent.



Scheme o

EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

(vii) isolute™ refers to silica (SiO_2) based columns with irregular particles with an average size of 50µm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd., Glamorgan, Wales, United Kingdom].

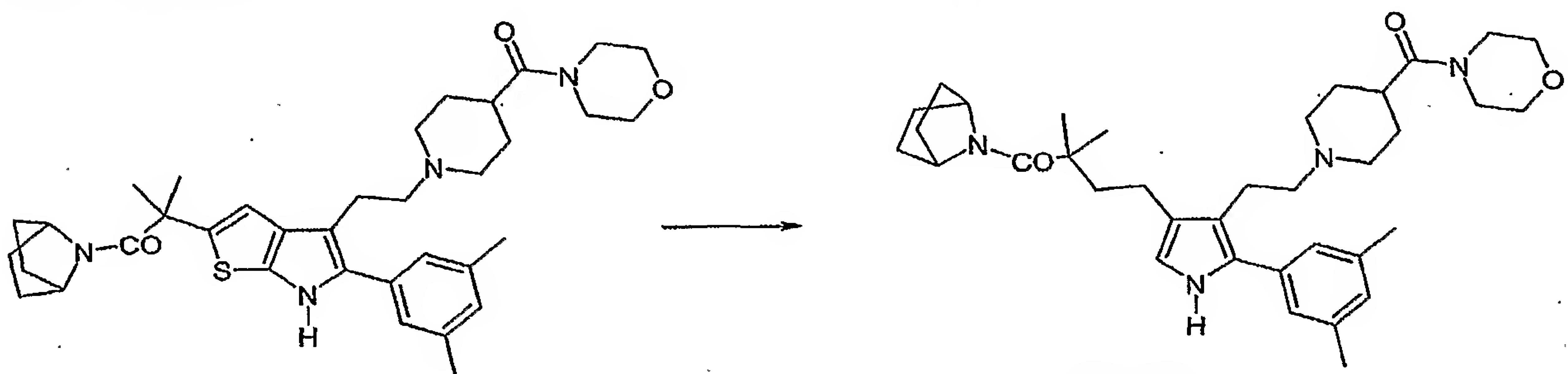
Abbreviations

Atm	atmospheres
boc	*t*-butoxycarbonyl
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulphoxide
DMF	dimethylformamide

DTAD	Di-*tert*-butyl azodicarboxylate
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
THF	tetrahydrofuran

Example 1

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(morpholin-4-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 1

R1

A suspension of **R1** (100 mg ; 0.162 mmol) in EtOH (50 ml) was treated with Raney-Nickel (5 g) and placed under an atmosphere of hydrogen (1.7 atm.). The mixture was stirred at room temperature for 16 hours. The mixture was filtered, the filtrate concentrated and the residue purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/10) to give **Example 1** as a white foam (50 mg).

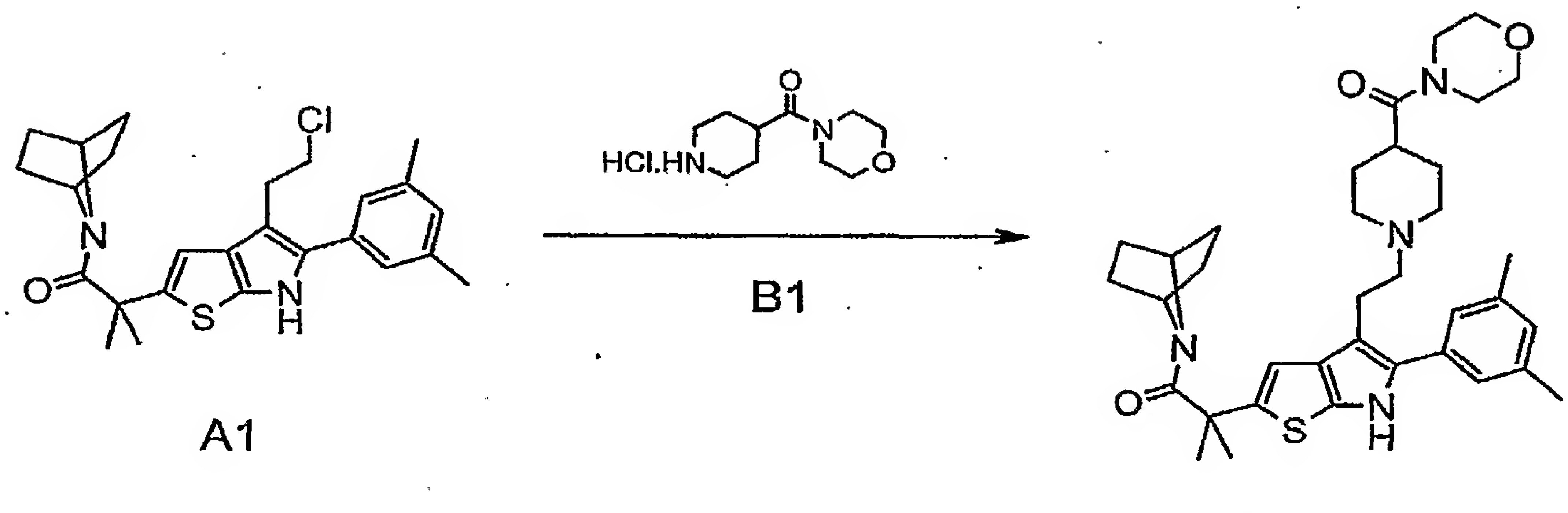
Yield : 52%

^{1}H NMR spectrum (CDCl3) : 1.29 (s, 6H) ; 1.47 (m, 4H) ; 1.67 (m, 2H) ; 1.79 (m, 4H) ; 1.88 (m, 4H) ; 2.07 (m, 2H) ; 2.33 (s, 6H) ; 2.44 (m, 3H) ; 2.5 (m, 2H) ; 2.77 (m, 2H) ; 3.04 (m, 2H) ; 3.48 (m, 2H) ; 3.62 (m, 2H) ; 3.67 (s br, 4H) ; 4.66 (s br, 2H) ; 6.56 (d, 1H) ; 6.90 (s, 1H) ; 7.03 (s, 2H) ; 7.92 (s br, 1H).

MS-ESI : 589 $[M+H]^+$

The starting material was prepared as follows:-

2-[1,1-dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{morpholinocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole (R1)



A1 B1 R1

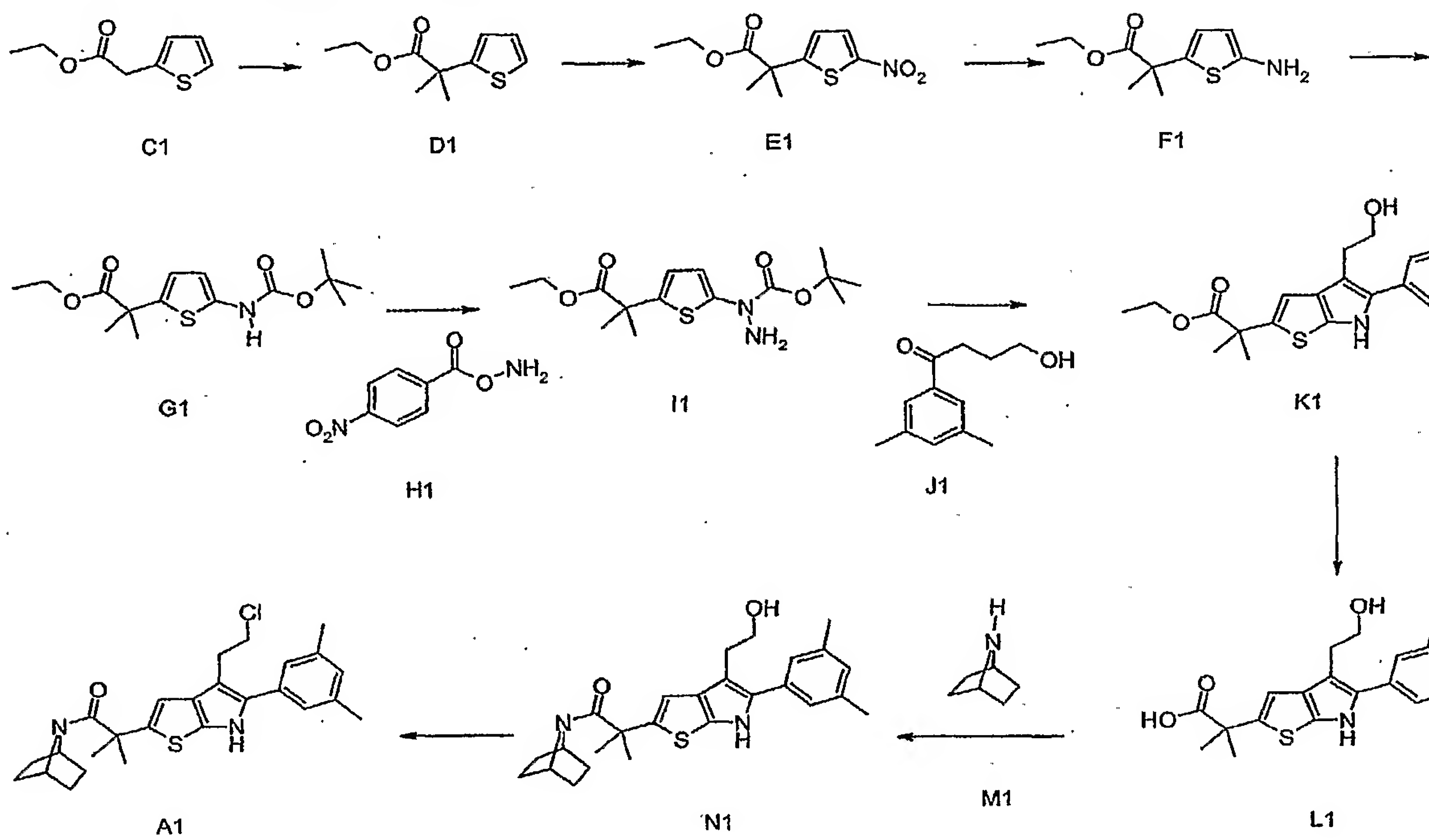
A mixture of **A1** (0.137 g ; 0.3 mmol), **B1** (0.150 g , 0.6 mmol), K_2CO_3 (0.125 g ; 0.9 mmol) and NaI (0.045 g ; 0.3 mmol) in dimethylacetamide (3 ml) was heated at 85°C under an argon atmosphere for 6 hours. The crude mixture was purified on preparative LC-MS (column Symetry C_{18}, AcOH buffer, H_2O-CH_3CN gradient) and the residue was evaporated and crystallised in a pentane-Et_2O mixture to give **R1** as a white solid.

Yield: 55 %

^{1}H NMR ($CDCl_3$) : 1.28 (m, 4H) ; 1.62 (s, 6H) ; 1.50-1.75 (m, 6H) ; 1.93 (m, 2H) ; 2.08 (m, 2H) ; 2.35 (s, 6H) ; 2.48 (m, 1H) ; 2.68 (m, 2H) ; 2.97 (br s, 2H) ; 3.09 (m, 2H) ; 3.50 (s, 2H) ; 3.62 (s, 2H) ; 3.68 (s, 4H) ; 4.12 (br s, 1H) ; 4.75 (br s, 1H) ; 6.75 (s, 1H) ; 6.94 (s, 1H) ; 7.06 (s, 2H) ; 8.13 (s, 1H).

MS-ESI: 617 $[M+H]^+$

The intermediate **A1** was prepared as follows:-



To a suspension of NaH (54 g ; 1.35 mol) and 18-crown-6 in THF (2 l) stirred at ambient temperature under an argon atmosphere, was added **C1** (100 g ; 0.588 mol) over a period of 30 minutes. After stirring overnight, the mixture was cooled to 0°C and methyl iodide was added dropwise. The mixture was stirred at 18°C for 3 hours, poured into a saturated solution of NH_4Cl and extracted with AcOEt. The organic phase was evaporated and purified by flash chromatography eluting with petroleum ether / ethyl acetate 95/5 to give **D1** as an oil.
Yield: 90 %
^{1}H NMR ($CDCl_3$): 1.20 (t, 3H) ; 1.63 (s, 6H) ; 4.10 (q, 2H) ; 6.92 (m, 2H) ; 7.17 (m, 1H).

Nitronium tetrafluoroborate (77.9 g ; 0.586 mol) was added at –55°C to a solution of **D1** (105.6 g ; 0.583 mol) in DME (1.5 l). The mixture was allowed to warm up to –10°C over 4 hours. After extraction with ethyl acetate, the organic phase was purified by flash chromatography, eluting with petroleum ether / AcOEt 95/5 to give **E1**.
Yield: 86 %
^{1}H NMR ($CDCl_3$): 1.23 (t, 3H ; 1.65 (s, 6H) ; 4.14 (q, 2H) ; 6.90 (d, 1H) ; 7.75 (d, 1H).

A suspension of **E1** (101.7 g ; 0.41 mol) and 10 % Pd/C (15 g) in a mixture of ethanol (700 ml) and ethyl acetate (300 ml) was hydrogenated under a hydrogen atmosphere

(1.5 atm.) for 5 hours. After filtration of the catalyst through celite, the residue was evaporated and redissolved in THF (900 ml). Di-*tert*-butyl dicarbonate (100 g ; 0.46 mol) was added and the mixture was refluxed for 16 hours. After evaporation of the solvents, the resulting solid was triturated with petroleum ether and filtered to give **G1**.

Yield: 68 %

^{1}H NMR ($CDCl_3$): 1.20 (t, 3H) ; 1.48 (s, 9H) ; 1.58 (s, 6H) ; 4.10 (q, 2H) ; 6.30 (m, 1H) ; 6.60 (m, 1H).

To a suspension of sodium hydride (44.6 g ; 1.12 mol) in DMF (700 ml) at 10°C, was added a solution of **G1** (290 g ; 930 mmol) in DMF (1 l) over a period of 5 minutes. The resulting orange suspension was allowed to warm to room temperature and stirred for 2 hours. The resulting solution was cooled to –5°C in an acetone/ice bath and a solution of **H1** (201 g ; 1.02 mol) in DMF (1.4 l) was added over a period of 1 hours. During this period additional DMF (1 l) was added to mobilise the thick precipitate which formed. The resulting suspension was allowed to warm to room temperature and stirred overnight after which HPLC showed no remaining starting material. The suspension was poured into water (6 litres) and extracted with diethyl ether (3 x 2 l). The organic extracts were combined and concentrated to approximately 3 litres and washed with water (4 x 1.5 l), a saturated solution of brine (1 l), dried over magnesium sulfate and evaporated to dryness to afford the free base as an off-white solid in quantitative yield. To a stirred solution of the free base (150 g ; 457 mmol) in diethyl ether (1.2 l) and heptane (600 ml) at 0°C, was added a 4.0M solution of HCl in 1,4-dioxane (145 ml ; 570 mmol) over a period of 1 hours. The resulting thick, white precipitate was collected by filtration, washed with a mixture of diethyl ether-heptane (1:1, 500 ml) and dried to a constant weight to afford the **I1.HCl** (160.3 g) as a white solid.

Yield: 96%

MS-ESI: 328 $[M+H]^+$

To a stirred solution of **I1** (141 g ; 380 mmol) in 2-butanol (1.3 l) was added **J1** (104 g ; 540 mmol) and zinc chloride (106 g ; 770 mmol). The resulting suspension was heated at 100°C for 8 hours after which HPLC showed no remaining starting material. The resulting dark brown solution was evaporated to dryness. The resulting dark brown residue was dissolved in CH_2Cl_2 (100 ml), filtered and the filtrate was purified by flash chromatography eluting with CH_2Cl_2 , ethyl acetate (9/1) to afford **K1** (98 g) as a brown solid.

Yield: 67%
MS-ESI: 386 $[M+H]^+$

To a stirred solution of **K1** (98 g ; 254 mmol) in ethanol (1.8 l) was added 1N NaOH (1.27 l ; 1.270 mol). The resulting solution was heated at 60°C for 4 hours after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature and the ethanol was evaporated. The resulting brown solution was cooled to 5°C and concentrated HCl was added dropwise with rapid agitation decreasing the pH to 1. The resulting precipitate was collected by filtration, washed to a neutral pH with water (3 x 1 l) and dried to a constant weight in a vacuum oven at 50°C to afford **L1** as a beige solid (68.3 g).
Yield: 75%
MS-ESI: 358 $[M+H]^+$

To a stirred solution of **L1** (35.7 g ; 100 mmol) and **M1** (57 g ; 150 mmol) in CH_2Cl_2 (1 l) at 0°C, was added DIPEA (70 ml ; 400 mmol) and solid HATU (57 g ; 150 mmol) over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours after which HPLC showed no remaining starting material. The reaction mixture was washed with a saturated aqueous solution of citric acid (350 ml), a saturated solution of sodium bicarbonate (350 ml) and water (3 x 350 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The resulting oily residue was triturated with ethyl acetate (100 ml) and the resulting precipitate collected by filtration and dried to a constant weight in a vacuum oven at 40°C to afford **N1** (31.4 g) as a beige solid.
Yield: 69%
MS-ESI: 437 $[M+H]^+$

To a stirred solution of **N1** (29.7 g ; 68.1 mmol) in CH_2Cl_2 (700 ml) at 0°C was added dropwise neat thionyl chloride (6 ml ; 81.7 mmol). The mixture was allowed to warm to room temperature and stirred for a period of 2 hours after which HPLC showed no remaining starting material. The reaction mixture was evaporated and purified by flash chromatography, eluting with CH_2Cl_2/AcOEt (9/1) to give **A1** as beige foam. The foam was triturated with diethyl ether (100 ml) and the resulting solid collected by filtration, washed with diethyl ether

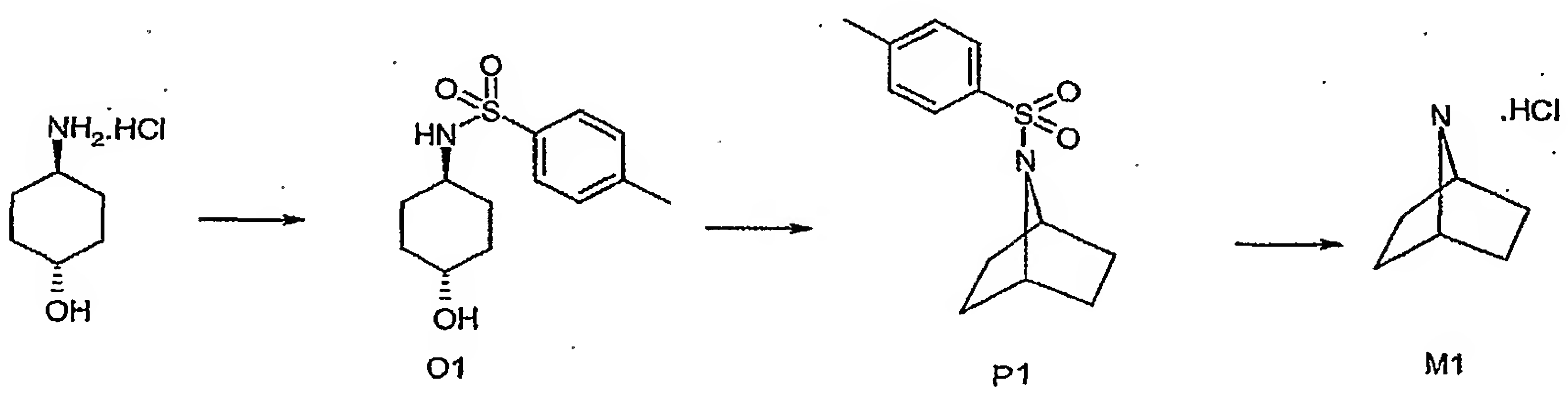
(2 x 50 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **A1** as a white solid (26.5 g).

Yield : 85%

MS-ESI: 454 $[M+H]^+$

^{1}H NMR (DMSO-d_6) 1.19-1.41 (m, 4H) ; 1.45-1.59 (m, 10H) ; 2.32 (s, 6H) ; 3.14 (t , 2H) ; 3.83 (t, 4H) ; 4.13 (br s, 1H) ; 4.43 (br s, 1H) ; 6.89-6.93 (two overlapping s, 2H) ; 7.08 (s, 2H).

The intermediate amine **M1** was synthesised as follows:-



To a stirred suspension of trans-4-aminocyclohexanol (300 g ; 1.98 mol) in isopropanol (3.5 l) at 0°C was added triethylamine (1.1 l ; 7.92 mol) followed by solid p-toluenesulfonyl chloride (377 g ; 1.98 mmol) over a period of 30 minutes. The reaction mixture was heated at 60°C for 2 hours after which HPLC showed no remaining starting material. The resulting suspension was cooled to room temperature and the precipitate of triethylamine hydrochloride removed by filtration. The filtrate was evaporated to dryness to afford a colourless oil which was dissolved in ethyl acetate (3 l), washed with 0.5N HCl (800 ml), water (1.5 l) and dried over $MgSO_4$. The solvent was evaporated on a rotary evaporator to afford **O1** (456.5 g) as a white crystalline solid.

Yield: 86%

MS-ESI: 270 $[M+H]^+$

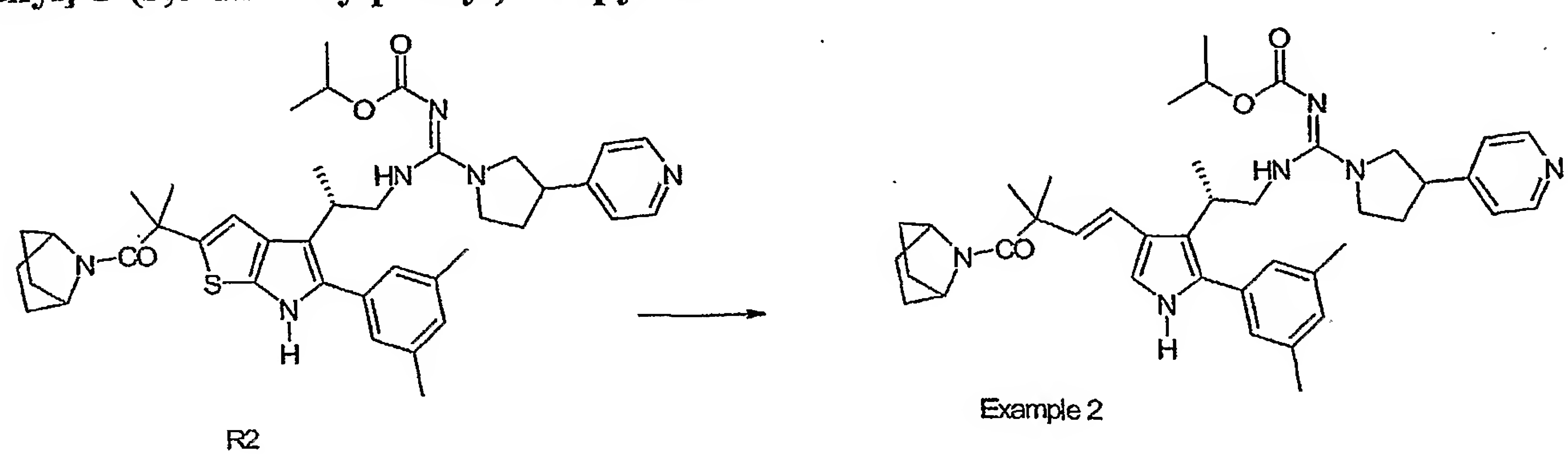
To a stirred solution of **O1** (600 g ; 2.23 mol) in THF (2 l) at –10°C in an ice/acetone bath, was added triphenylphosphine (700 g ; 2.67 mol) followed by di-*tert*-butyl azodicarboxylate (DTAD) (564 g; 2.45 mol) in THF (1.5 l) over a period of 1.5 hours maintaining the internal temperature below 10°C. The ice/acetone bath was removed and reaction mixture was allowed to warm to room temperature over a period of 1.5 hours after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue was crystallised from hot MeOH (2.8 l). The resulting crystalline suspension was

cooled to 0°C and the crystals collected by filtration, washed with cold MeOH (2 x 200 ml) and dried to a constant weight in a vacuum oven to afford **P1** (378.2 g) as a white crystalline solid routinely contaminated with approximately 10% (w/w) of triphenylphosphine oxide.
Yield: 68%
MS-ESI: 252 $[M+H]^+$

In two separate batches:- To a stirred solution of **P1** (380 g ; 1.51 mol) in THF (3 l) at 0°C was added solid pellets of lithium aluminium hydride (229.4 g ; 6.04 mol) over a period of 2 hours under nitrogen. The resulting grey suspension was allowed to warm to room temperature and stirred for 4 days after which HPLC showed no remaining starting material. The reaction mixture was diluted with THF (1 l), cooled to 0°C and solid sodium sulfate decahydrate was added over a period of 2 hours with rapid agitation. When the effervescence had subsided, the resulting suspension was filtered and the filtrate acidified with gaseous HCl affording a thick white precipitate which was collected by filtration, washed with THF (2 x 500 ml) and dried to a constant weight to afford **M1** (batch 1: 86.8 g ; 43%) (batch 2: 97.3 g ; 49%) as a white solid. The filter cakes obtained from the first filtration were suspended in 6N NaOH (400 ml) and filtered. The filtrate was extracted with diethyl ether (4 l). The organic layer was acidified with gaseous HCl affording a thick white precipitate which was collected by filtration, washed with diethyl ether (2 x 500 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **M1.HCl** (105.9 g) as a white solid.
Yield: 72%
^{1}H NMR (DMSO d_6) 1.57 (m, 4H) ; 1.86 (m, 4H) ; 4.12 (s, 2H) ; 8.8-9.05 (s br, 1H).

Example 2

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)but-2-en-1-yl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 2 was synthesised by the method used for preparing Example 1, except that MeOH was used as the solvent. The following quantities of starting material and conditions were used: **R2** (600 mg ; 0.85 mmol) ; MeOH (30 ml) ; RaNi (12 g) ; hydrogen (1.7 atm.) ; 16 hours. **Example 2** was obtained as a yellow foam (120 mg).

Chromatography : Ammonia in MeOH(7N)/CH_2Cl_2 (1/20)

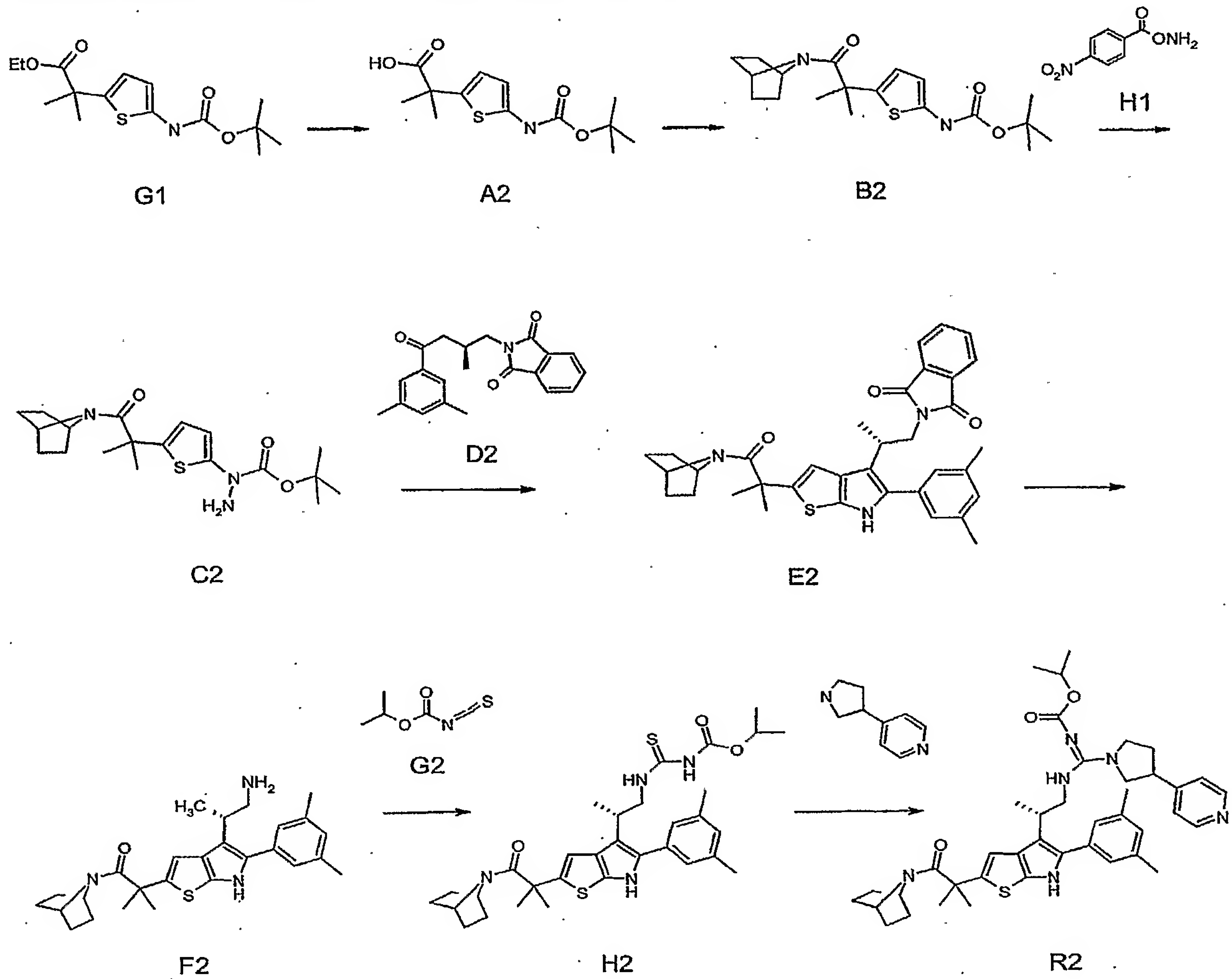
Yield : 21%

^1H NMR spectrum ($CDCl_3$) : 1.2-1.26 (m, 9H) ; 1.35-1.4 (m, 12H) ; 1.75 (m, 4H) ; 2.2 (m, 1H) ; 2.3 (s, 6H) ; 3.05-3.5 (m, 7H) ; 3.65 (m, 1H) ; 4.63 (s br, 2H) ; 4.84 (m, 1H) ; 6.03 (dd, 1H) ; 6.45 (dd, 1H) ; 6.83 (d, 1H) ; 6.93 (m, 3H) ; 7.06 (dd, 2H) ; 8.01 (s, 1H) ; 8.52 (m, 2H).

MS-ESI : 679 $[M+H]^+$

The starting material was prepared as follows:-

2-(1,1-dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)--6*H*-thieno[2,3-*b*]pyrrole (R2)



A solution of **G1** (50 g ; 0.16 mol) and 2N NaOH (160 ml) in EtOH (300 ml) was refluxed for 1 hours 30 minutes. After evaporation to dryness, the residue was partitioned between water and ether. The aqueous layer was acidified with saturated citric acid and extracted with EtOAc to give after evaporation a solid, which was triturated in pentane and filtered to give **A2** as a solid.

Yield: 100%

^{1}H NMR (DMSOd$_6$): 1.48 (m, 15H) ; 6.30 (d, 1H) ; 6.59 (d, 1H).

A solution of **A2** (172 g ; 0.6 mol), EDCI (172 g ; 0.9 mol) and DMAP (22 g ; 0.18mol) in CH_2Cl_2 (1.5 l) was stirred under an argon atmosphere for 10 minutes. Solid **M1.HCl** (88 g ;

0.66 mol) was then added and the mixture was stirred overnight at ambient temperature. After evaporation to dryness, the residue was partitioned between EtOAc and water. The organic phase was evaporated and the solid residue was triturated with diethyl ether, filtered, washed with diethyl ether and dried to a constant weight in a vacuum oven to afford **B2** (153.7 g) as a beige solid.

Yield: 70.5%

^{1}H NMR (DMSOd$_6$): 1.28 (m, 4 H) ; 1.44 (m, 19H) ; 4.0 (s br, 1H) ; 4.4 (s br, 1H) ; 6.33 (d, 1H) ; 6.53 (d, 1H) ; 10.29 (s, 1H).

A suspension of **B2** (153.7 g ; 0.42 mol) in DMF (1.2 l) was added under an argon atmosphere to a suspension of NaH 60 % (20.2 g ; 0.5 mol) in DMF (400 ml). The mixture was stirred 1.5 hours, cooled to 5°C and a solution of **H1** (92.1 g ; 0.5 mol) in 1,4-dioxane (4 l) was added. The reaction mixture was stirred at ambient temperature overnight. After filtration of the insoluble, the filtrate was evaporated to dryness and the residue was partitioned between Et_2O and water. The organic phase was mostly evaporated and the solid precipitate was filtered, washed with a saturated solution of $NaHCO_3$, pentane and dried to a constant weight in a vacuum oven to to give **C2** (127.2 g) as a white solid.

Yield: 80 %

^{1}H NMR ($CDCl_3$): 1.31 (m, 4 H) ; 1.56 (s, 15H) ; 1.6 (m, 4H) ; 4.0 (s br, 1H); 4.51 (s, 2H) ; 4.7 (d, 2H) ; 6.54 (d, 1H) ; 6.70 (s br, 1H).

To a stirred suspension of **C2** (17 g ; 45 mmol) and **D2** (22.5 g ; 67.0 mmol) in 2-butanol (50 ml) was added a 4M solution of HCl in 1,4-dioxane (22.5 ml ; 90.0 mmol). The resulting thick suspension was heated at 90°C for 1 hour after which HPLC showed no remaining starting material. The resulting dark brown solution was evaporated to dryness on a rotary evaporator and the residue was dissolved in CH_2Cl_2 and purified by flash chromatography on silica gel eluting with EtOAc/hexanes (10-50% EtOAc) to afford **E2** (16 g) as a white solid.

Yield: 54%

^{1}H NMR ($CDCl_3$) : 1.26-1.40 (m, 7H) ; 1.57 (s, 6H) ; 1.63-1.83 (m, 4H) ; 2.32 (s, 6H) ; 3.66 (m, 1H) ; 3.87 (m, 2H) ; 4.20 (s br, 1H) ; 4.75 (s br, 1H) ; 6.86 (s, 1H) ; 6.92 (s, 1H) ; 6.98 (s, 2H) ; 7.67 (m, 2H) ; 7.74 (m, 2H) ; 8.03 (s, 1H) .

MS-ESI: 580 $[M+H]^+$

To a stirred suspension of **E2** (14 g ; 24 mmol) in EtOH (300 ml) at room temperature, was added neat hydrazine monohydrate (12 ml ; 240 mmol). The reaction mixture was stirred at room temperature for 16 hours after which HPLC showed no remaining starting material. The resulting precipitate was collected by filtration, washed with EtOH (2 x 20 ml) and the filtrate was evaporated to dryness on a rotary evaporator and dried to a constant weight under high vacuum to afford **F2** (10.9 g) as a yellow foam which was used without further purification.

Yield: 100%

^{1}H NMR ($CDCl_3$) : 1.27-1.36 (m, 7H) ; 1.43-1.53 (m, 10H) ; 2.34 (s, 6H) ; 3.06 (m, 1H) ; 3.23 (m, 1H) ; 3.28 (m, 1H) ; 4.10 (s br, 1H) ; 4.50 (s br, 1H) ; 6.87 (s, 1H) ; 6.96 (s, 1H) ; 7.07 (s, 2H) .

MS-ESI: 450 $[M+H]^+$

To a solution of **G2** (0.098 g ; 0.66 mmol) in CH_2Cl_2 (1.5 ml) at 0°C was added a solution of **F2** (300 mg ; 0.66 mmol) in CH_2Cl_2 (1.5 ml). The mixture was stirred at ambient temperature for 90 minutes and extracted. The organic layer was evaporated and purified by flash chromatography, eluting with CH_2Cl_2/AcOEt (50/50) to give **H2**.

Yield: 90 %

^{1}H NMR ($CDCl_3$): 1.2 (m, 6H) ; 1.2-1.35 (m, 4H) ; 1.38 (d, 3H) ; 1.50-1.80 (m, 4H) ; 1.55 (s, 6H) ; 2.35 (s, 6H) ; 3.45 (m, 1H) ; 1.78 (m, 1H) ; 4.00 (m, 1H) ; 4.10 (s br 1H) ; 4.75 (s br, 1H) ; 4.87 (m, 1H) ; 6.80 (s, 1H) ; 6.96 (s, 1H) ; 7.07 (s, 2H) ; 7.72 (s, 1H) ; 8.10 (s, 1H) ; 9.54 (s, 1H).

MS-ESI: $[M+H]^+$ 595

To a solution of **H2** (325 mg; 0.54 mmol) in CH_2Cl_2 (10 ml) at 0°C was added under an argon atmosphere 4-pyrrolidin-3-yl pyridine (122 mg; 0.82 mmol), EDC (158 mg; 0.82 mmol) and DIPEA (0.142 ml; 0.82 mmol). The mixture was stirred at 0°C for 15 minutes allowed to warm up and stirred for 24 hours at ambient temperature. The reaction mixture was extracted with CH_2Cl_2. The organic layer was evaporated and the crude material was purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/20) to give **R2** as a solid.

Yield: 55 %.

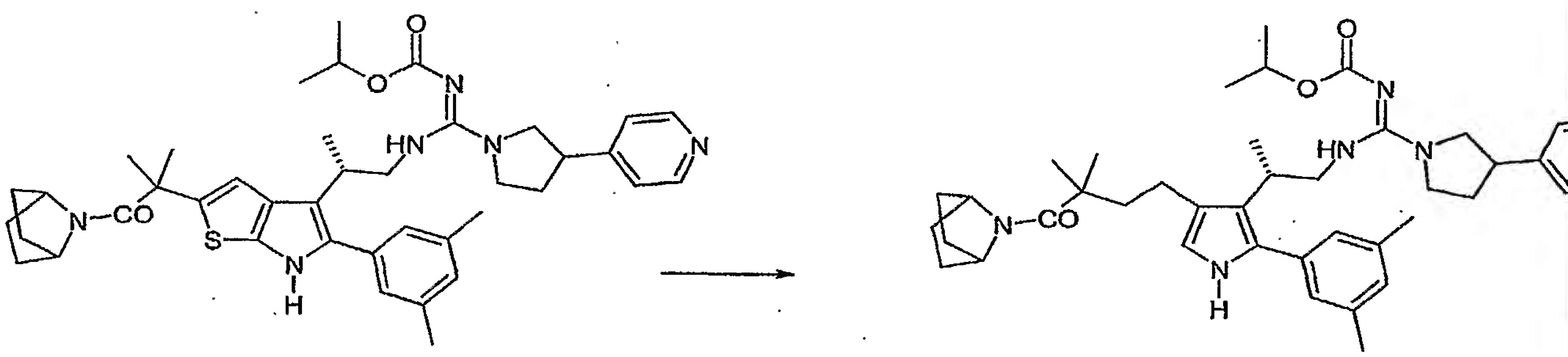
^{1}H NMR ($CDCl_3$): 1.2 (m, 6H) ; 1.2-1.3 (m, 4H) ; 1.4 (m, 3H) ; 1.5-1.68 (m, 4H) ; 1.55 (s, 6H) ; 1.7-1.9 (m, 1H) ; 2.1-2.2 (m, 1H) ; 2.28 (m, 6H) ; 3.02-3.5 (m, 7H) ; 3.6 (m, 1H) ; 4.05

(s br, 1H) ; 4.7 (s br, 1H) ; 4.82 (m, 1H) ; 6.72 (s, 1H) ; 6.9 (m, 1H) ; 7.0 (s, 1H) ; 7.05 (d, 2H) ; 8.20 (s, 1H) ; 8.50 (d, 2H).

MS-ESI: $[M+H]^+$ 709

Example 3

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R2 Example 3

Example 3 was synthesised by the method used for preparing Example 1. The following quantities of starting material and conditions were used: **R2** (300 mg ; 0.425 mmol) ; EtOH (50 ml) ; RaNi (10 g) ; hydrogen (1.5 atm.) ; 3 days. **Example 3** was obtained as a yellow foam (121 mg).

Chromatography : Ammonia in MeOH(7N)/CH_2Cl_2 (1/10)

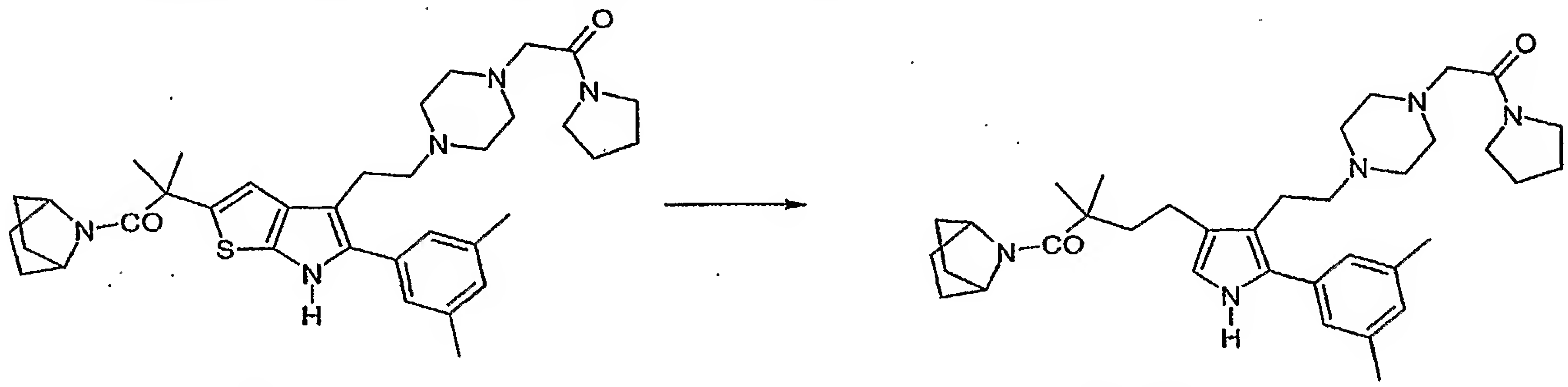
Yield : 42%

^{1}H NMR spectrum ($CDCl_3$) : 1.12-1.26 (m, 9H) ; 1.29 (s, 6H) ; 1.35 (t, 2H) ; 1.46 (m, 4H) ; 1.77 (m, 4H) ; 1.89 (m, 2H) ; 2.2 (m, 1H) ; 2.3 (s, 6H) ; 2.5 (m, 2H) ; 3.05-3.45 (m,7H) ; 3.65 (m, 1H) ; 4.65 (s br, 2H) ; 4.84 (m, 1H) ; 6.57 (s, 1H) ; 6.92 (m, 3H) ; 7.08 (dd, 2H) ; 7.87 (s, 1H) ; 8.52 (m, 2H).

MS-ESI : 681 $[M+H]^+$

Example 4

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R4 Example 4

Example 4 was synthesised by the method used for preparing Example 1, except that MeOH was used as solvent and the reaction was carried out with no hydrogen atmosphere. The following quantities of starting material and conditions were used: **R4** (300 mg ; 0.488 mmol) ; MeOH (20 ml) ; RaNi (0.5 g) ; 3 days. **Example 4** was obtained as a pale yellow foam (102 mg).

Chromatography : Ammonia in MeOH(7N)/CH_2Cl_2 (1/20)

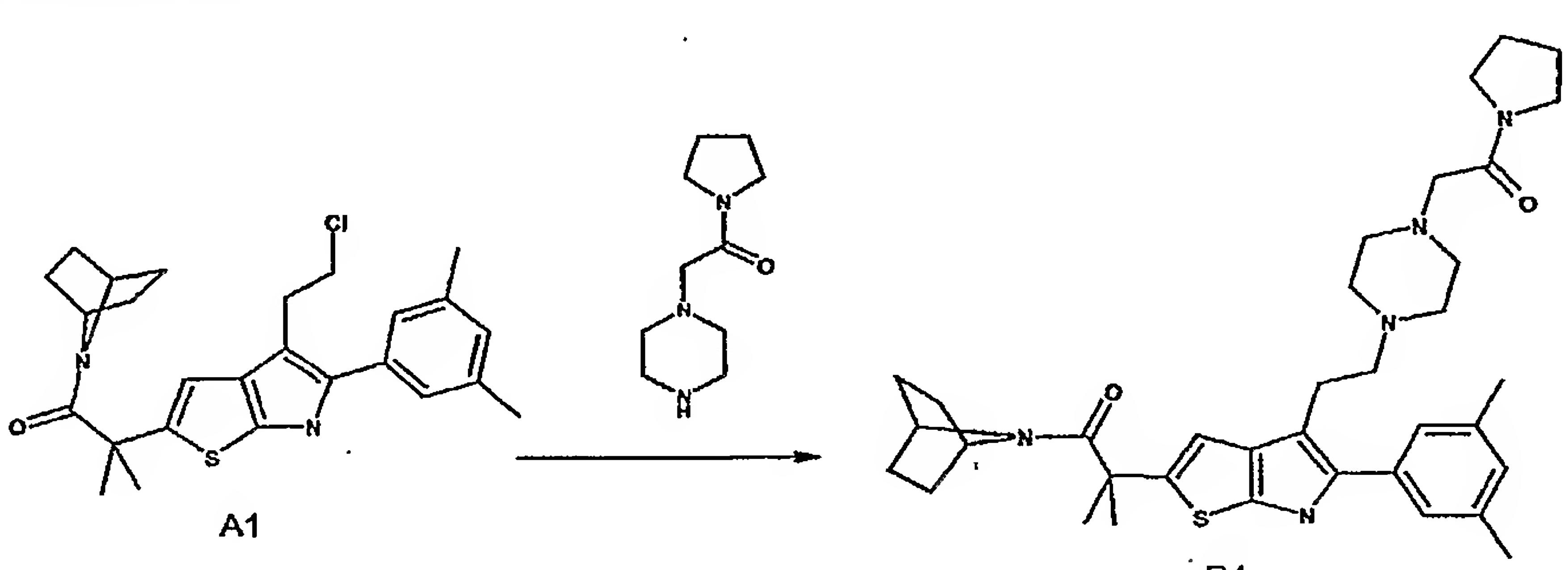
Yield : 35%

^{1}H NMR spectrum ($CDCl_3$) : 1.29 (s, 6H) ; 1.47 (m, 4H) ; 1.79 (m, 4H) ; 1.87 (m, 4H) ; 1.94 (t, 2H) ; 2.32 (s, 6H) ; 2.44 (m, 2H) ; 2.51 (m, 2H) ; 2.59 (m br, 8H) ; 2.77 (m, 2H) ; 3.11 (s, 2H) ; 3.48 (m, 4H) ; 4.66 (s br, 2H) ; 6.55 (d, 1H) ; 6.89 (s, 1H) ; 7.02 (s, 2H) ; 7.92 (s br, 1H).

MS-ESI : 588 $[M+H]^+$

The starting material was prepared as follows:-

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole



A1 R4

A mixture of **A1** (see Example 1) (182 mg; 0.4 mmol), N-(pyrrolidinocarbonylmethyl)-piperazine (95 mg, 0.48 mmol), NaI (72 mg; 0.48 mmol) and K_2CO_3 (67 mg; 0.48 mmol) in acetonitrile (4 ml) was heated at 80°C under argon atmosphere for 8 hours. The crude mixture was evaporated and purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/20) to give after trituration in ether/pentane **R4** as a solid.

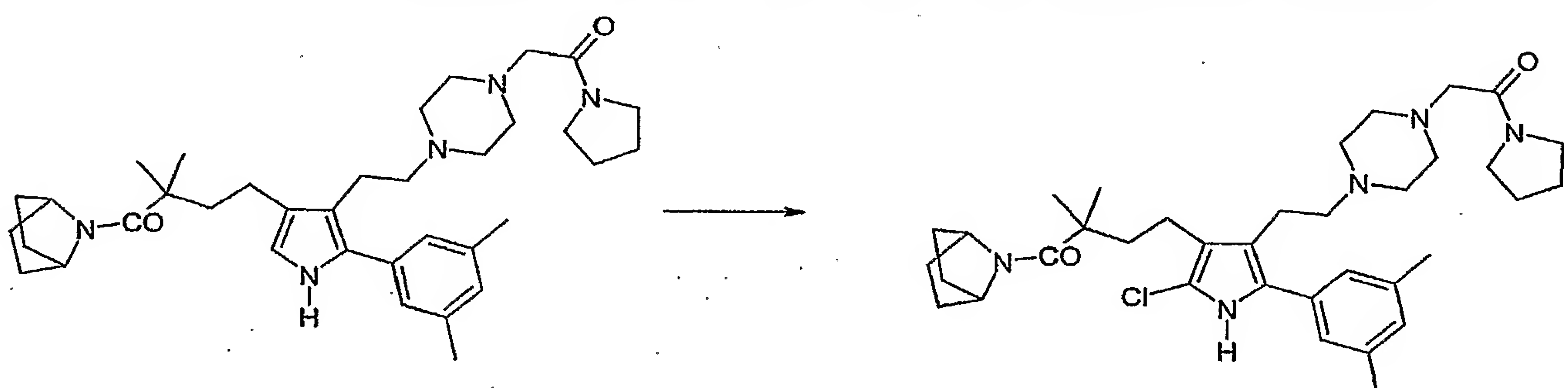
Yield: 42%

^{1}H NMR ($CDCl_3$) : 1.15-1.4 (m, 6H) ; 1.45-1.75 (m, 6H) ; 1.59 (s, 6H) ; 1.8-2 (m, 4H) ; 2.32 (s, 6H) ; 2.45-2.75 (m, 6H) ; 2.9-3 (m, 2H) ; 3.1 (s, 2H) ; 3.44-3.5 (m, 4H) ; 4-4.2 (m, br, 1H) ; 4.6-4.8 (m, br, 1H) ; 6.72 (s, 1H) ; 6.92 (s, 1H) ; 7.04 (s, 2H) ; 8.13 (s, 1H).

MS-ESI: 616 $[M+H]^+$

Example 5

2-Chloro-3-[3,3-dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(morpholin-4-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 4 Example 5.

A solution of **Example 4** (100 mg ; 0.17 mmol) in THF (0.5 ml) was treated with N-chlorosuccinimide (23 mg ; 0.17 mmol). The mixture was stirred at room temperature for 16h, concentrated, and the residue purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/20) to give **Example 5** as a pink foam (23 mg).

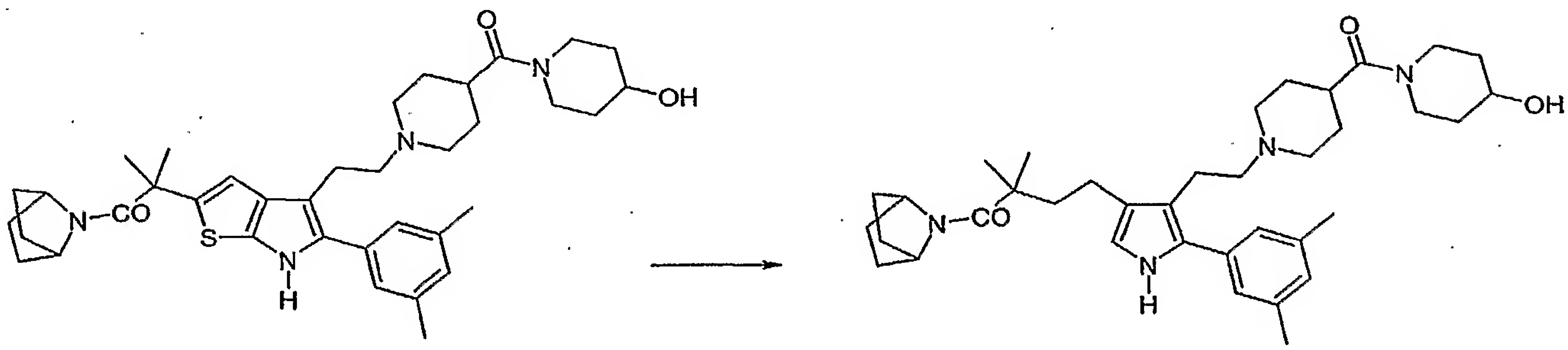
Yield : 22%

^{1}H NMR spectrum ($CDCl_3$) : 1.3 (s, 6H) ; 1.47 (m, 4H) ; 1.78 (m, 4H) ; 1.85 (m, 4H) ; 1.94 (t, 2H) ; 2.32 (s, 6H) ; 2.42 (m, 2H) ; 2.5 (m, 2H) ; 2.58 (m br, 8H) ; 2.73 (m, 2H) ; 3.11 (s, 2H) ; 3.48 (m, 4H) ; 4.66 (s br, 2H) ; 6.90 (s, 1H) ; 6.99 (s, 2H) ; 7.83 (s br, 1H).

MS-ESI : 623 and 625 $[M+H]^+$

Example 6

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(4-hydroxypiperidin-1-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R6 Example 6

Example 6 was synthesised by the method used for preparing Example 1. The following quantities of starting material and conditions were used: **R6** (250 mg ; 0.4 mmol) ; EtOH (140 ml) ; RaNi (8.9 g) ; hydrogen (1.5 atm.) ; 3 hours. **Example 6** was obtained as a cream foam (127 mg).

Chromatography : Increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0-10% MeOH)

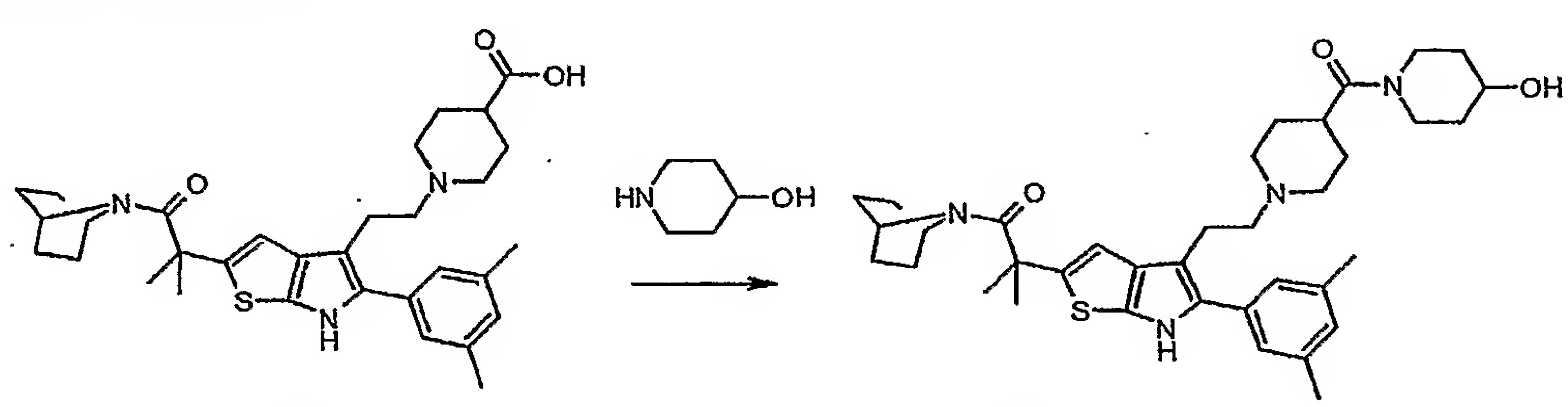
Yield : 53%

^1H NMR spectrum ($CDCl_3$) : 1.3 (s, 6H) ; 1.35-2.2 (m, 19H) ; 2.34 (s, 6H) ; 2.4-3.4 (m, 12H) ; 3.75 (m,1H) ; 3.9 (m, 1H) ; 4.10 (m, 1H) ; 4.66 (s br, 2H) ; 6.55 (d, 1H) ; 6.9 (s, 1H) ; 7.02 (s, 2H) ; 7.94 (s, 1H).

MS-ESI : 603 $[M+H]^+$

The starting alcohol **R6** was prepared as follows:-

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{4-hydroxy piperidin-1-ylcarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole



A6 R6

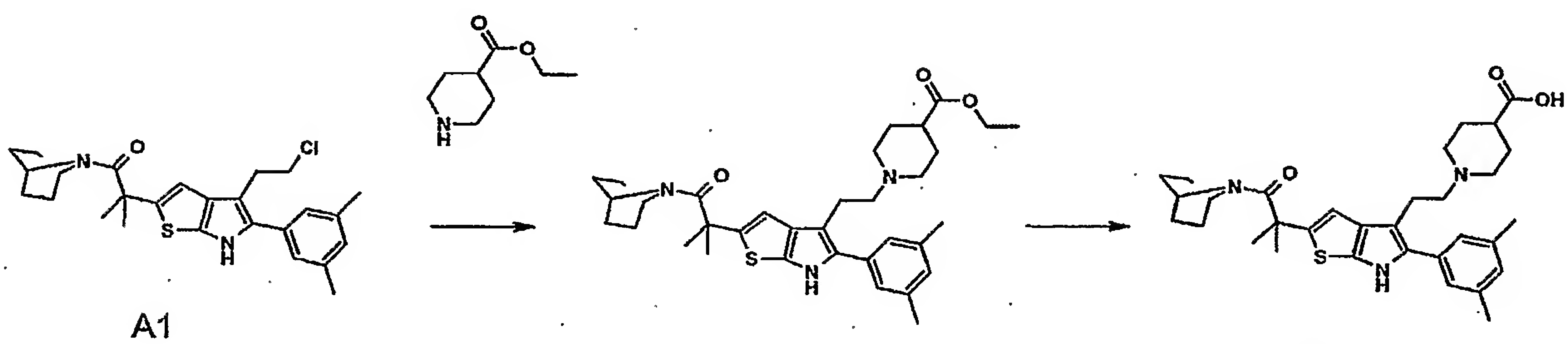
A mixture of **A6** (547 mg ; 1 mmol), HATU (608 mg ; 1.6 mmol) and DIPEA (520 µl ; 3 mmol) in CH_2Cl_2 (10ml) was treated with 4-hydroxypiperidine (202 mg ; 2 mmol) and stirred at ambient temperature for 0.5 hours. The mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The residue was purified by flash chromatography eluting with increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0-10% MeOH) to give **R6** as a white solid (520 mg).

Yield : 83%

^{1}H NMR (DMSO d_6) : 1.29 (m, 8H) ; 1.51 (s, 6H) ; 1.5-1.8 (m, 10H) ; 2.05 (m, 1H) ; 2.31 (s, 6H) ; 2.5 (m, 2H) ; 2.86 (m, 2H) ; 2.96 (m, 2H) ; 3.16 (m, 1H); 3.68 (m, 2H) ; 3.89 (m, 1H) ; 4.1 (s br, 1H) ; 4.55 (s br, 1H) ; 4.73 (d, 1H) ; 6.80 (s, 1H) ; 6.92 (s, 1H) ; 7.09 (m, 2H).

MS-ESI: 631 $[M+H]^+$

The starting material was prepared as follows:-



A mixture of **A1** (see Example 1) (4.55g ; 0.01 mol), 4-ethoxycarbonyl piperidine (2.36g ; 0.015 mol), triethylamine (1.53ml ; 0.011mol) and NaI (1.5g ; 0.01mol) in DMA (45 ml) was heated at 110°C under argon atmosphere for 4 hours . After extraction with EtOAc and evaporation, the mixture was purified by flash chromatography, eluting with increasingly polar mixtures of EtOAc/hexanes (80-100% EtOAc) to give **B6**.

Yield: 62%

^{1}H NMR ($CDCl_3$): 1.25 (t, 3H) ; 1.2-1.45 (m, 4H) ; 1.5-1.8 (m, 4H) ; 1.62 (s, 6H) ; 1.7-2 (m, 4H) ; 2.05-2.15 (m, 2H) ; 2.25-2.35 (m, 1H) ; 2.35 (s, 6H) ; 2.64-2.67 (m, 2H) ; 2.93-2.98 (m, 4H) ; 4.13 (q, 2H) ; 4.0-4.2 (br m, 1H) ; 4.6-4.8 (br m, 1H) ; 6.74 (s, 1H) ; 6.94 (s, 1H) ; 7.07 (s, 2H) ; 8.13 (s, 1H).

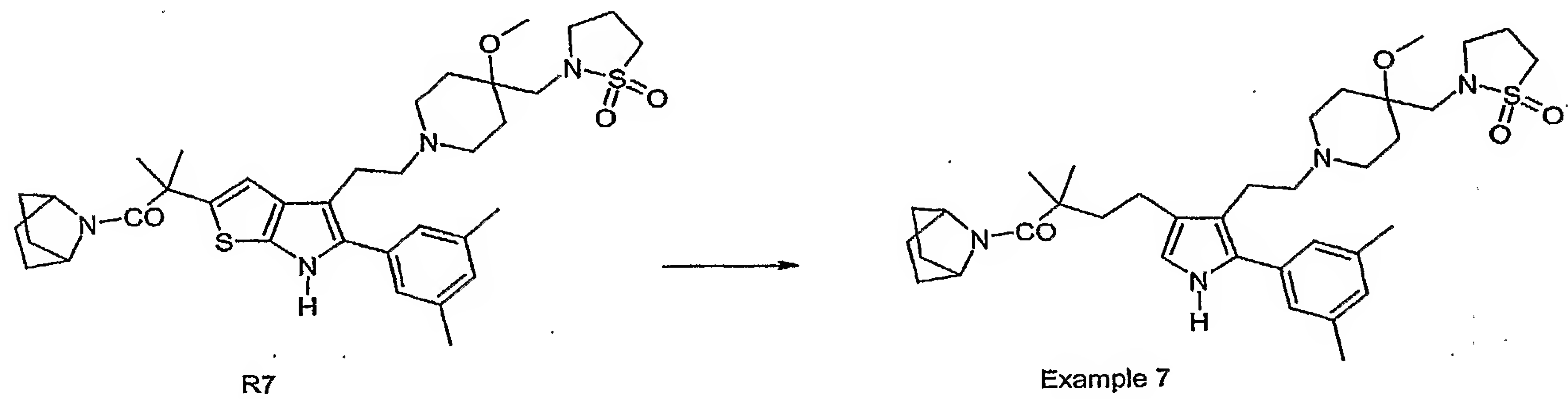
A solution of **B6** (3.61g ; 0.627 mmol) in 2N NaOH (5ml) and EtOH (100 ml) was heated at 60°C for 2 hours. After extraction with CH_2Cl_2/MeOH (1/1)and evaporation, the residue was triturated in ether to give **C6** as a solid.

Yield : 93%

^{1}H NMR (DMSO d_6, AcOH) : 1.30 (m, 4H) ; 1.40-1.70 (m, 4H) ; 1.53 (s, 6H) ; 1.80-2.00 (m, 4H) ; 2.05 (m, 2H) ; 2.34 (s, 6H) ; 2.65 (m, br, 1H) ; 3.14 (m, 2H) ; 3.27 (m, 2H) ; 3.30-3.60 (m, 2H) ; 4.10 (m, br, 1H) ; 4.50 (m, br, 1H) ; 6.96 (m, 2H) ; 7.09 (m, 2H).

Example 7

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[2-{4-(1,1-dioxo-isothiazolidin-2-ylcarbonyl)-4-methoxy-piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 7 was synthesised by the method for preparing Example 1, except that a mixture of MeOH and EtOH was used as solvent. The following quantities of starting material and conditions were used: **R7** (65 mg ; 0.1 mmol) ; EtOH (3 ml) ; MeOH (3 ml) ; RaNi (5.7 g) ; hydrogen (1.5 atm.) ; 2 hours. **Example 7** was obtained as a white foam (50 mg).

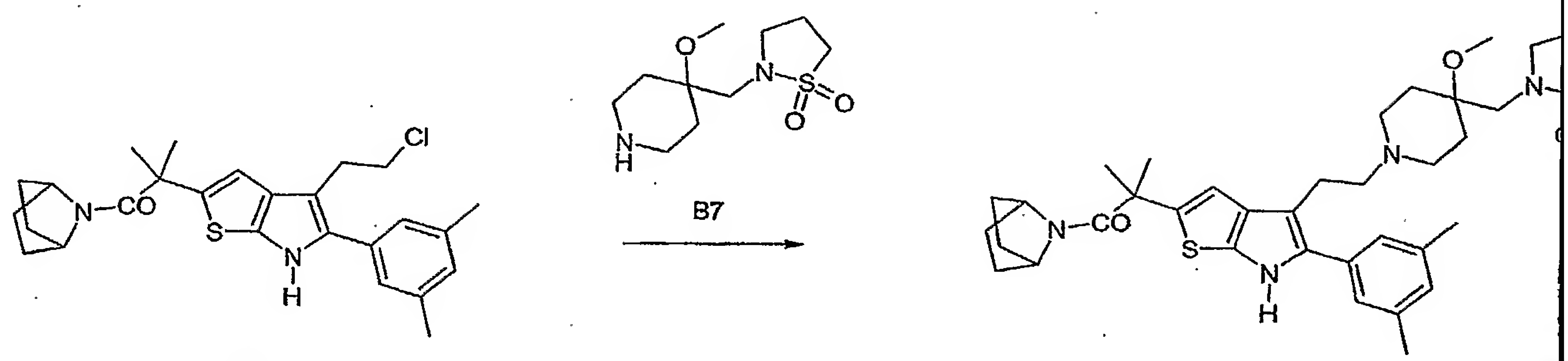
Chromatography : Increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0-10% MeOH)

Yield : 81%

^{1}H NMR spectrum ($CDCl_3$) : 1.29 (s, 6H) ; 1.47 (m, 4H) ; 1.62 (s, 4H) ; 1.79 (m, 4H) ; 1.87 (m, 4H) ; 2.34 (s, 6H) ; 2.39 (m, 2H) ; 2.44 (m, 2H) ; 2.51 (m, 2H) ; 2.65 (m, 2H) ; 2.77 (m, 2H) ; 3.06 (s br, 2H) ; 3.1 (t, 2H) ; 3.22 (s,3H) ; 3.42 (t, 2H) ; 4.66 (s br, 2H) ; 6.55 (d, 1H) ; 6.9 (s, 1H) ; 7.02 (s, 2H) ; 7.93 (s, 1H).

MS-ESI : 639 $[M+H]^+$

R7 was prepared as follows:-



A1 B7 R7

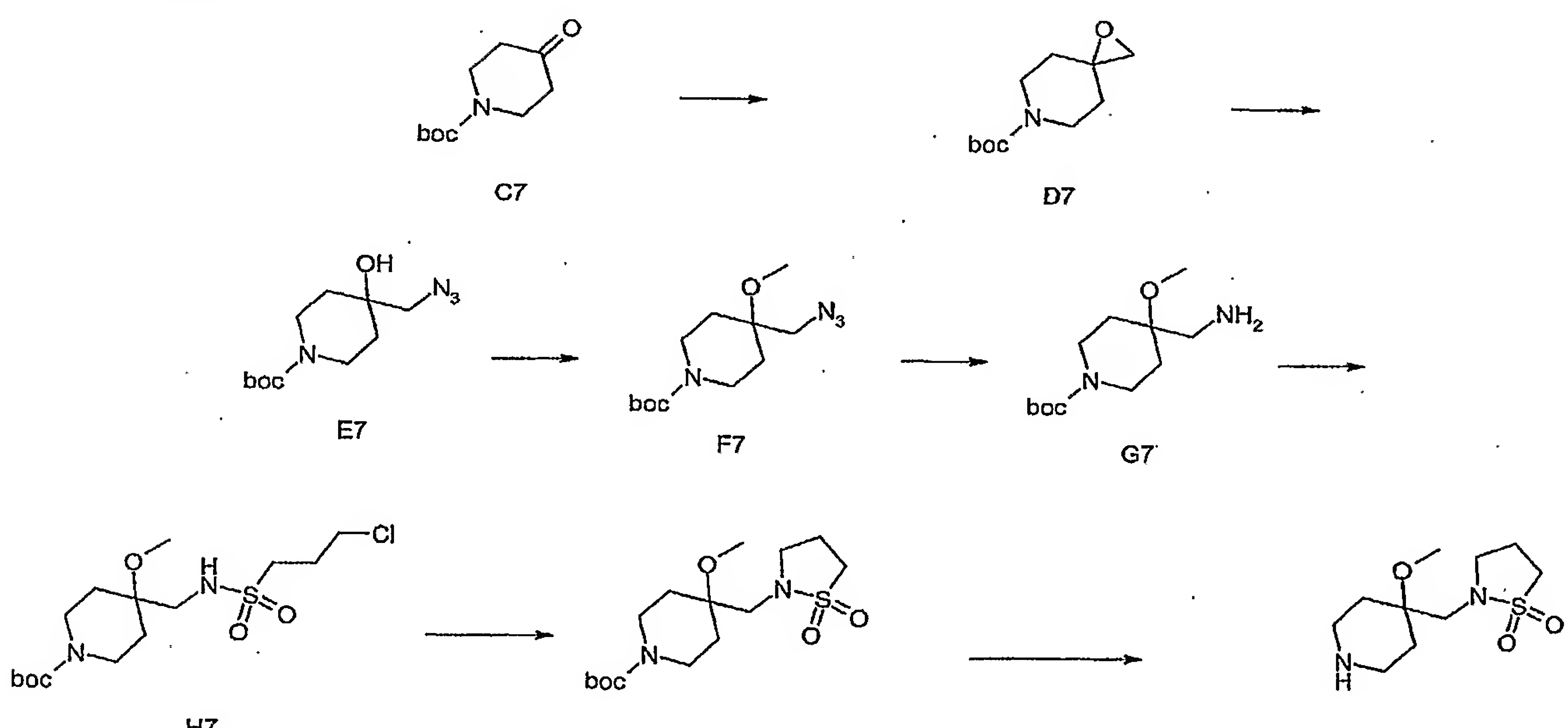
A solution of **A1** (see Example 1) (260 mg ; 0.57 mmol) and **B7** (325 mg ; 1.15 mmol) in DMF (1.5 ml) and acetonitrile (3 ml) under argon was treated with K_2CO_3 (239 mg ; 1.72 mmol). The mixture was heated at 90°C for 3 hours. The mixture was cooled, treated with pentane and filtered. The residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (5% MeOH) to give **R7** as a white foam (260 mg).

Yield : 68%

^{1}H NMR spectrum ($CDCl_3$) : 1.32 (s br, 4H) ; 1.62 (s, 14H) ; 1.88 (m, 2H) ; 2.35 (s, 6H) ; 2.41 (m, 2H) ; 2.68 (m, 4H) ; 2.95 (m, 2H) ; 3.06 (s,2H) ; 3.1 (t, 2H) ; 3.22 (s, 3H) ; 3.43 (t, 2H) ; 4.10 (s br, 1H) ; 4.7 (s br, 1H) ; 6.75 (s, 1H) ; 6.94 (s, 1H) ; 7.06 (s, 2H) ; 8.13 (s, 1H).

MS-ESI : 667 [M+H]$^+$

B7 was prepared as follows:-



C7 D7 E7 F7 G7 H7 I7 B7

A 60% suspension of NaH in oil (230 mg ; 5.5 mmol) in DMSO (6 ml) under argon was

treated with trimethylsulphonium iodide (1.26 g ; 5.75 mmol) at 5°C. The mixture was stirred for 30 minutes and **C7** (1.0g ; 5 mmol) was added. The mixture was stirred for 1 hour at room temperature. The mixture was partitioned between water and diethyl ether. The diethyl ether was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/ CH_2Cl_2 (0-30% EtOAc) to give **D7** (870 mg).

Yield : 82%

^{1}H NMR spectrum ($CDCl_3$) : 1.47 (s, 9H) ; 1.50 (m, 2H) ; 1.78 (m, 2H) ; 2.69 (s, 2H) ; 3.43 (m, 2H) ; 3.71 (m, 2H).

A solution of **D7** (3.9g ; 18.3 mmol) in MeOH (100 ml) and water (20 ml) was treated with sodium azide (5.95 g ; 91.5 mmol) and ammonium chloride (1.96 g ; 36.6 mmol). The mixture was heated under reflux for 15 hours. The solvents were removed by evaporation and the residue partitioned between water and CH_2Cl_2. The CH_2Cl_2 was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (20-30% EtOAc) to give **E7** (4.24 g).

Yield : 90%

^{1}H NMR spectrum ($CDCl_3$) : 1.46 (s, 9H) ; 1.50 (m, 2H) ; 1.62 (m, 2H) ; 1.79 (s, 1H) ; 3.14 (m, 2H) ; 3.3 (s, 2H) ; 3.85 (m, 2H).

A solution of **E7** (4.2 g ; 16.4 mmol) in THF (20 ml) under argon was treated with a 60% suspension of NaH in oil (868 mg ; 18.9 mmol). Methyl iodide (1.23 ml ; 19.7 mmol) was added dropwise followed by crown ether 15-5 (30 drops). The mixture was stirred overnight, the THF evaporated and the residue partitioned between water and EtOAc. The residue was purified by flash chromatography with EtOAc/hexanes (20% EtOAc) to give **F7** (4.15 g).

Yield : 94%

^{1}H NMR spectrum ($CDCl_3$) : 1.42 (m, 2H) ; 1.46 (s, 9H) ; 1.81 (m, 2H) ; 3.1 (m, 2H) ; 3.25 (m, 5H) ; 3.8 (m, 2H).

A solution of **F7** (3.45 g ; 12.9 mmol) in EtOH (100 ml) and EtOAc (10 ml) was hydrogenated (1.2 atm. H_2) over Pd/C (520 mg ; 10 %) for 2.5 hours. The mixture was filtered to give **G7** (2.94 g).

Yield : 93%

^1H NMR spectrum ($CDCl_3$) : 1.35 (m, 2H) ; 1.46 (s, 9H) ; 1.76 (m, 2H) ; 2.66 (s, 2H) ; 3.1 (m, 2H) ; 3.19 (s, 3H) ; 3.8 (m, 2H).

A solution of **<u>G7</u>** (750 mg ; 3.07 mmol) in EtOAc (25 ml) was cooled to 0°C and treated successively with K_2CO_3 (470 mg ; 3.38 mmol) and 3-chloropropanesulphonyl chloride (411 µl ; 3.38 mmol). The mixture was allowed to warm to room temperature overnight and the solvent evaporated. The residue was purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/20) to give **<u>H7</u>** (1.02 g).

Yield : 86%

^1H NMR spectrum ($CDCl_3$) : 1.43 (m, 2H) ; 1.45 (s, 9H) ; 1.82 (m, 2H) ; 2.29 (m, 2H) ; 3.15 (m, 4H) ; 3.2 (s, 3H) ; 3.23 (m, 2H) ; 3.69 (t, 2H) ; 3.8 (m, 2H) ; 4.41 (t, 1H).

A solution of **<u>H7</u>** (1.0 g ; 2.6 mmol) in toluene (35 ml) was cooled to 0°C. A 60% suspension of NaH in oil (156 mg ; 3.9 mmol) was added and the mixture heated at 90° overnight. The solvent was evaporated and the residue purified by flash chromatography eluting with ammonia in MeOH(7N)/CH_2Cl_2 (1/20) to give **<u>I7</u>** (910 mg).

Yield : 99%

^1H NMR spectrum ($CDCl_3$) : 1.45 (s, 9H) ; 1.49 (m, 2H) ; 1.79 (m, 2H) ; 2.36 (m, 2H) ; 3.05 (s, 2H) ; 3.11 (m, 4H) ; 3.23 (s, 3H) ; 3.4 (m, 2H) ; 3.75 (t, 2H).

A solution of **<u>I7</u>** (910 mg ; 2.61 mmol) in 1,4-dioxane (7 ml) and CH_2Cl_2 (1 ml) was treated with a mixture of 1,4-dioxane (3.3 ml) and conc. HCl (0.7 ml). The mixture was stirred overnight and the solvents removed to give **<u>B7</u>** as a white solid (745 mg).

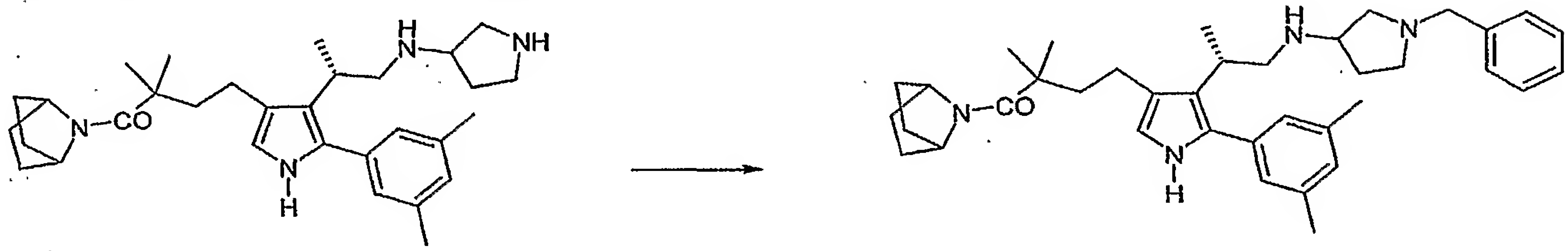
Yield : 99%

^1H NMR spectrum (DMSO d_6) : 1.61 (m, 2H) ; 1.90 (m, 2H) ; 2.23 (m, 2H) ; 2.88 (m, 2H) ; 3.03 (s, 2H) ; 3.12 (m, 4H) ; 3.15 (s, 3H) ; 3.33 (2H).

MS-ESI : 249 $[M+H]^+$

Example 8

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-{1-benzyl-pyrrodin-3-ylamino}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R8 Example 8

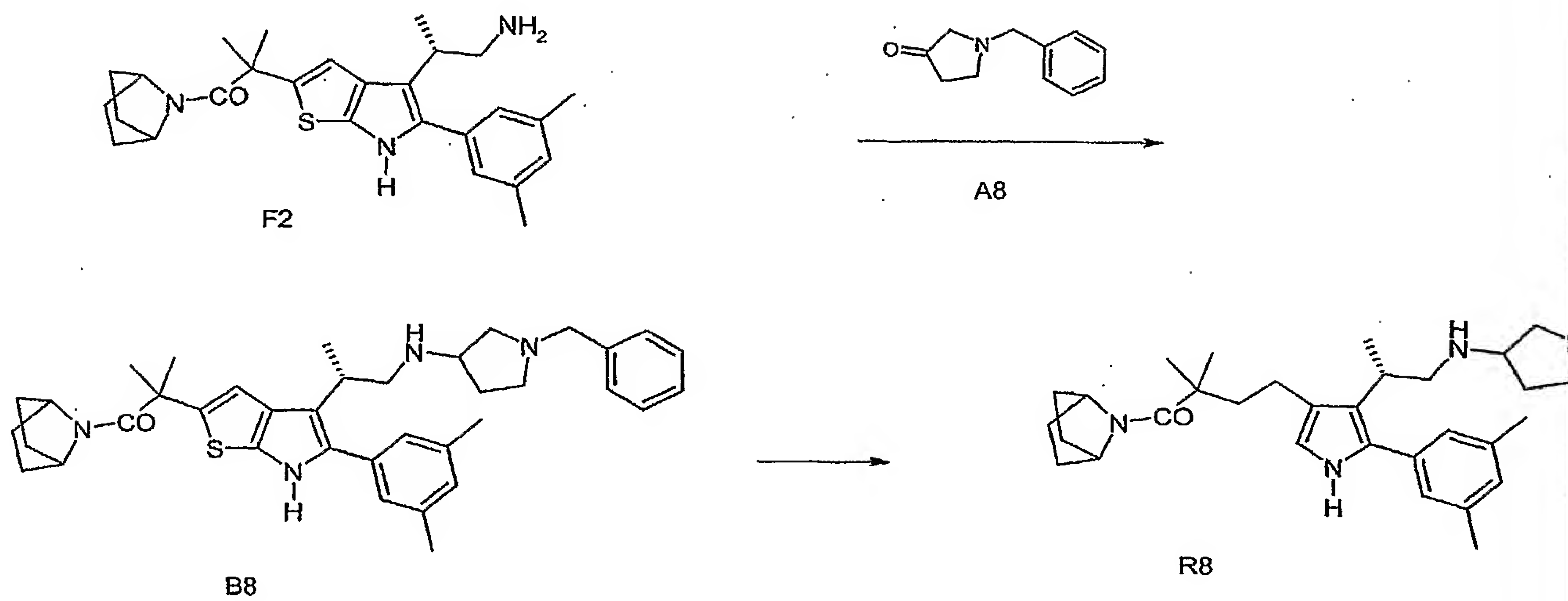
A solution of **R8** (100 mg ; 0.2 mmol) in MeOH (3 ml) was treated with benzaldehyde (22 µl; 0.22 mmol) and three drops of acetic acid. The mixture was cooled to 0°C. Sodium cyanoborohydride (14 mg ; 0.22 mmol) was added and the mixture was allowed to warm to room temperature for 2 hours. A saturated aqueous solution of $NaHCO_3$ was added, the MeOH evaporated and the mixture extracted into CH_2Cl_2. The solvent was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0-10% MeOH) to give **Example 8** as a rose foam (76 mg).

Yield : 64%

^{1}H NMR spectrum ($CDCl_3$) : 1.3 (m, 9H) ; 1.46 (m, 4H) ; 1.77 (m, 1H) ; 1.78 (m, 4H) ; 1.88 (m, 2H) ; 1.91 (m, 1H) ; 2.29 (m, 1H) ; 2.31 (d, 6H) ; 2.33-2.81 (m, 7H) ; 3.18 (m, 2H) ; 3.6 (m, 2H) ; 4.66 (s br, 2H) ; 6.56 (s, 1H) ; 6.91 (s, 1H) ; 6.97 (d, 2H) ; 7.3 (s, 5H) ; 7.83 (s br, 1H).

MS-ESI : 581 $[M+H]^+$

The starting material was prepared as follows:-



A solution of **F2** (300 mg ; 0.67 mmol) in MeOH (2 ml) was treated with N-benzyl-3-pyrrolidone (120 µl ; 0.73 mmol) and acetic acid (5 drops). Sodium cyanobobohydride (46 mg ; 0.73 mmol) was added and the mixture stirred overnight. A saturated aqueous solution of $NaHCO_3$ was added and the MeOH evaporated. The mixture was extracted into CH_2Cl_2. The solvent was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (0-10% MeOH) to give **B8** as a faint rose foam (250 mg).

Yield : 62%

^{1}H NMR spectrum ($CDCl_3$) : 1.31 (d, 3H) ; 1.4 (m, 4H) ; 1.53 (m, 1H) ; 1.61 (t, 6H) ; 1.65 (m, 4H) ; 1.99 (m, 1H) ; 2.21 (m, 1H) ; 2.33 (d, 6H) ; 2.5 (m, 2H) ; 2.7-2.9 (m, 3H) ; 3.22 (m, 2H) ; 3.57 (m, 2H) ; 4.1 (s br, 1H) ; 4.75 (s br, 1H) ; 6.75 (d, 1H) ; 6.94 (s, 1H) ; 7.08 (s, 2H) ; 7.25 (m, 5H) ; 8.12 (s, 1H).

MS-ESI : 609 $[M+H]^+$

A suspension of **B8** (215 mg ; 0.35 mmol) in EtOH (5 ml) and MeOH (5 ml) was treated with Raney-Nickel (10 g) and placed under an atmosphere of hydrogen (1.7 atm.). The mixture was stirred at room temperature for 2 hours. The mixture was filtered, the filtrate concentrated and the residue purified by flash chromatography eluting with increasingly polar mixtures of ammonia in MeOH(7N)/CH_2Cl_2 (0-10% MeOH) to give **R8** as a white foam (100 mg).

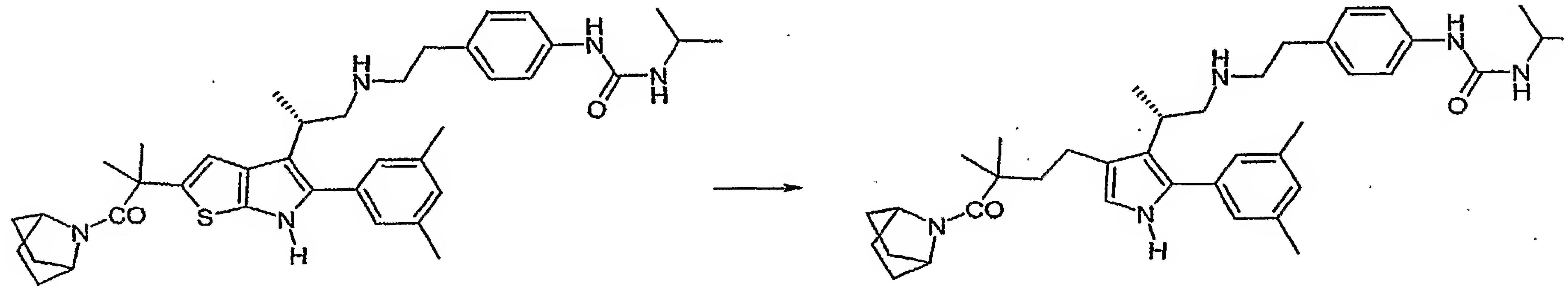
Yield : 58%

[1]H NMR spectrum (CDCl3) : 1.26 (d, 3H) ; 1.29 (s, 6H) ; 1.47 (m, 4H) ; 1.79 (m, 4H) ; 1.8-1.9 (m, 4H) ; 2.33 (d, 6H) ; 2.51 (m, 2H) ; 2.65-3.15 (m, 8H) ; 4.67 (s br, 2H) ; 6.56 (d, 1H) ; 6.94 (s, 1H) ; 7.0 (s, 2H) ; 7.85 (s br, 1H).

MS-ESI : 491 $[M+H]^+$

Example 9

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-(2-{4-N-isopropylureidophenyl}ethylamino)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R9 Example 9

Example 9 was synthesised by the method used for preparing Example 1, except that a mixture of MeOH and EtOH was used as solvent. The following quantities of starting material and conditions were used: R9 (40 mg ; 0.06 mmol) ; EtOH (3 ml) ; MeOH (3 ml) ; RaNi (1.5 g) ; 16 hours. Example 9 was obtained as a beige foam (20 mg).

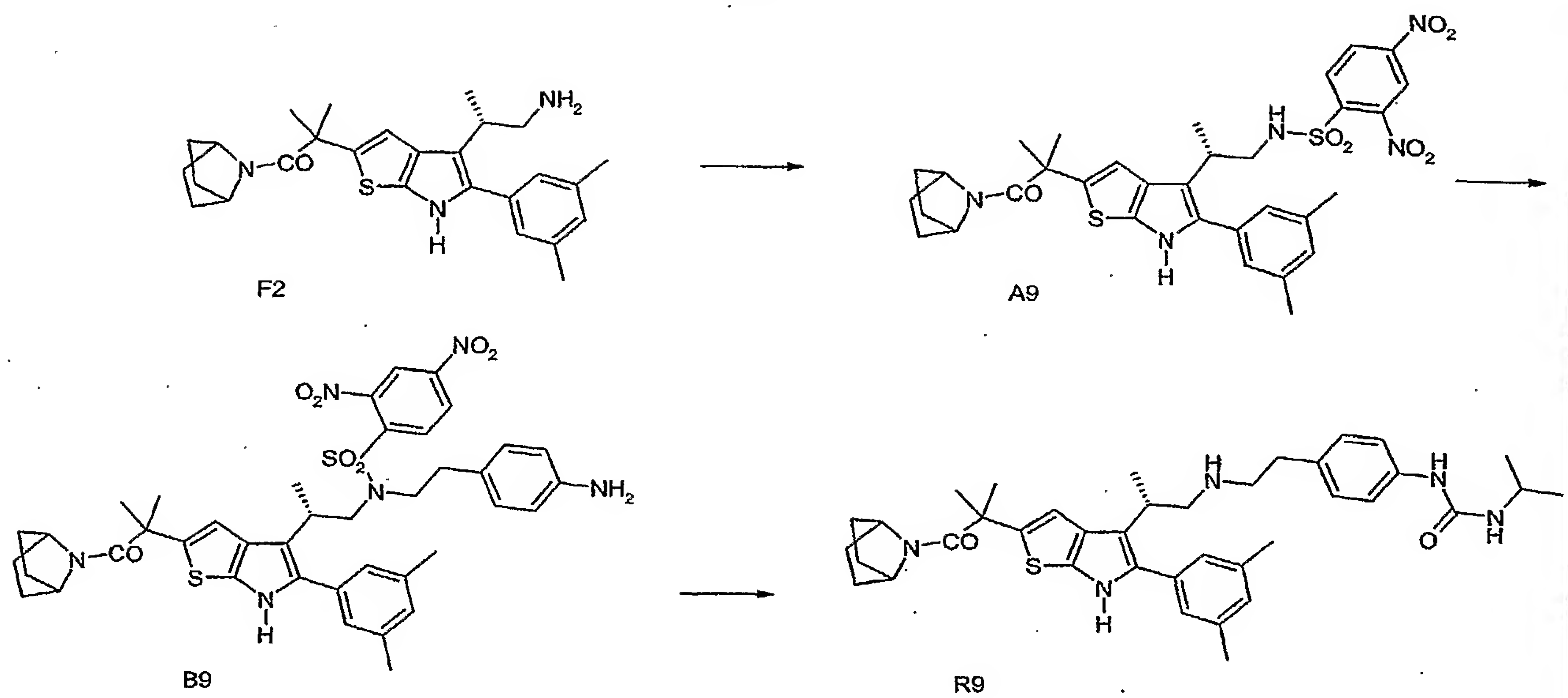
Chromatography : $MeOH/CH_2Cl_2$ (0-10% MeOH)

Yield : 53%

[1]H NMR spectrum ($CDCl_3$) : 1.18 (m, 6H) ; 1.28 (m, 6H) ; 1.32 (d, 3H) ; 1.45 (m, 4H) ; 1.76 ; (m, 4H) ; 1.85 (m, 2H) ; 2.28 (s, 6H) ; 2.4 (t, 2H) ; 2.64 (m, 1H) ; 2.77 (m, 2H) ; 2.87 (t, 1H) ; 2.9 (m, 1H) ; 3.05 (m, 1H) ; 3.32 (m, 1H) ; 3.95 (m, 1H) ; 4.62 (s br, 2H) ; 5.8 (s br, 1H) ; 6.54 (d, 1H) ; 6.74 (d, 2H) ; 6.77 (s, 2H) ; 6.88 (s, 1H) ; 7.22 (d, 2H) ; 8.1 (s br, 1H) ; 8.69 (s, 1H).

MS-ESI : 626 $[M+H]^+$

The starting material was prepared as follows:-



A solution of **F2** (1.5 g ; 3.34 mmol) in CH_2Cl_2 (20 ml) under argon at 0°C was treated with collidine (485 µl ; 3.67 mmol). 2,4-Dinitrophenyl sulphonyl chloride (978 mg ; 3.67 mmol) was added. The mixture was stirred for 1 hours and evaporated. The residue was purified by flash chromatography with EtOAc/CH_2Cl_2 (20% EtOAc) to give **A9** as a brown powder (1.9 g).

Yield : 84%.

^{1}H NMR spectrum ($CDCl_3$) : 1.31 (m, 4H) ; 1.33 (d, 3H) ; 1.62 (s, 6H) ; 1.65 (m, 4H) ; 2.27 (s, 6H) ; 2.91 (m, 1H) ; 3.55 (m, 1H) ; 3.65 (m, 1H) ; 4.1 (s br, 1H) ; 4.7 (s br, 1H) ; 5.34 (s, 1H) ; 6.69 (s, 1H) ; 6.72 (s, 2H) ; 6.81 (s, 1H) ; 8.12 (d, 1H) ; 8.19 (s, 1H) ; 8.22 (d, 1H) ; 8.33 (dd, 1H).

A solution of **A9** (130 mg ; 0.19 mmol) and 3-(2-hydroxyethyl)aniline (40 mg ;0.29 mmol) in THF (10 ml) was cooled to 0°C. Ph_3P (301 mg ; 1.15 mmol) and then DTAD (177 mg ; 0.77 mmol) were added and the mixture was stirred for 2 hours. Water was added, the THF was evaporated and the residue partitioned between water and CH_2Cl_2. The residue was purified by flash chromatography with increasingly polar solutions of EtOAc/ CH_2Cl_2 (0-20% EtOAc) to give crude **B9** (530 mg) contaminated with Ph_3PO.

MS-ESI : 800 $[M+H]^+$

A solution of crude **B9** (530 mg) in CH_2Cl_2 (10 ml) was treated with 2-propyl isocyanate (332 µl ; 3.4 mmol). The mixture was heated at 45°C for 2h, cooled and partitioned between water

and CH_2Cl_2. The residue was taken up in n-propylamine (5 ml), stirred for 1hour and evaporated. The residue was purified by flash chromatography with increasingly polar solutions of EtOAc/CH_2Cl_2 (0-100% EtOAc) and then MeOH/CH_2Cl_2 (0-10% MeOH) to give **R9** (60 mg).

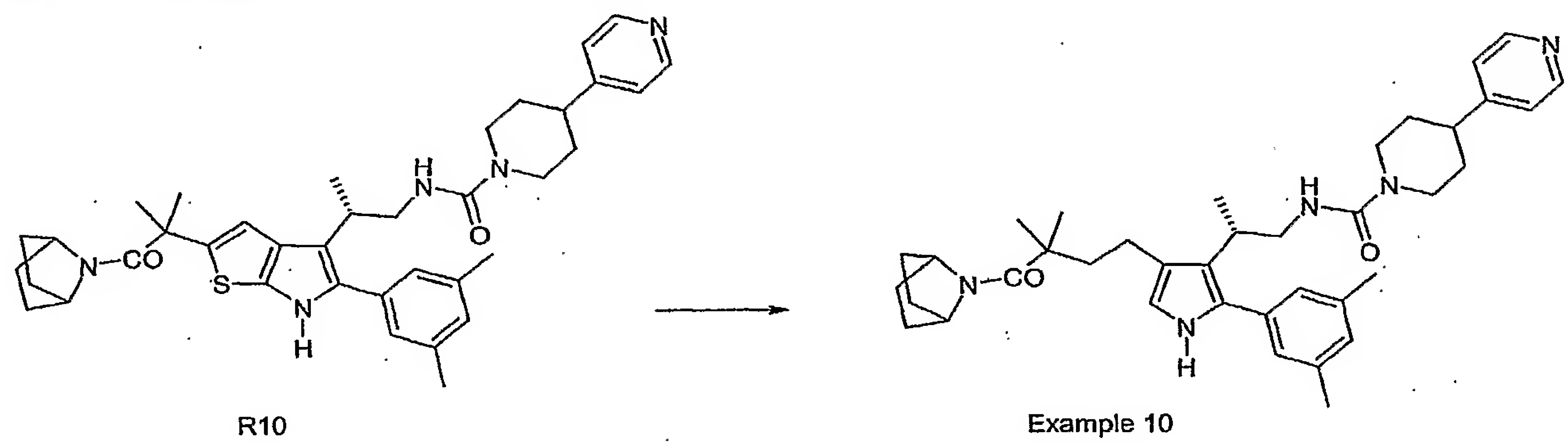
Yield : 49%, for the previous two steps.

^{1}H NMR spectrum ($CDCl_3$) : 1.19 (m, 6H) ; 1.31 (d, 3H) ; 1.32 (m, 4H) ; 1.63 (s, 6H) ; 1.65 (m, 4H) ; 2.32 (s, 6H) ; 2.55 (m, 3H) ; 2.8 (m, 2H) ; 3.03 (m, 1H) ; 3.27 (m, 1H) ; 3.99 (m, 1H) ; 4.1 (s br, 1H) ; 4.7 (s br, 1H) ; 5.34 (s, 1H) ; 6.61 (d, 2H) ; 6.64 (s, 1H) ; 6.89 (s, 1H) ; 6.94 (s, 2H) ; 7.05 (d, 2H) ; 7.5 (s br, 1H) ; 9.6 (s, 1H).

MS-ESI : 654 $[M+H]^+$

Example 10

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-{4-(pyrid-4-yl)piperidin-1-ylcarbonylamino}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 10 was synthesised by the method used for preparing Example 1, except that a mixture of MeOH and EtOH was used as solvent. The following quantities of starting material and conditions were used: **R10** (190 mg ; 0.3 mmol) ; EtOH (5 ml) ; MeOH (5 ml) ; RaNi (2 g) ; hydrogen (1.5 atm.) ; 16 hours. **Example 10** was obtained as a cream foam (80 mg).

Chromatography : MeOH/CH_2Cl_2 (0-5% MeOH)

Yield : 44%

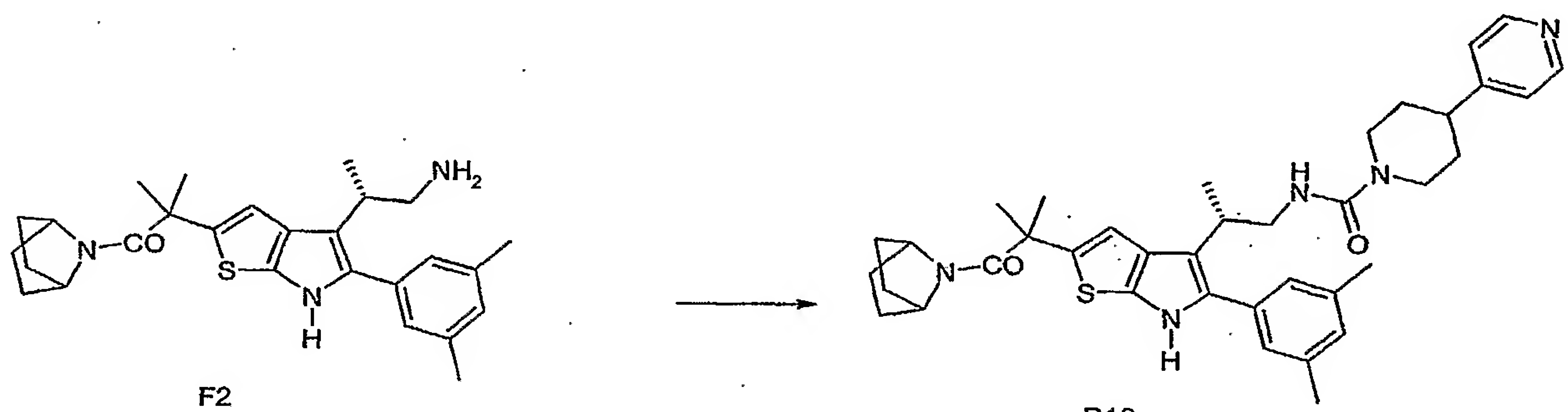
^{1}H NMR spectrum ($CDCl_3$) : 1.3 (m, 9H) ; 1.46 (m, 4H) ; 1.74 (m, 8H) ; 1.9 (m, 2H) ; 2.31 (s, 6H) ; 2.55 (m, 3H) ; 2.72 (m, 2H) ; 3.21 (m, 2H) ; 3.64 (m, 1H) ; 3.80 (m,1H) ; 3.95 (m, 1H) ;

4.44 (d, 1H) ; 4.66 (s br, 2H) ; 6.59 (d, 1H) ; 6.92 (s, 1H) ; 6.98 (s, 2H) ; 7.05 (d, 2H) ; 7.89 (s, 1H) ; 8.50 (d, 2H).

MS-ESI : 610 $[M+H]^+$

The starting material was prepared as folows:-

<u>2-(1,1-dimethyl-2-oxo-2- azabicyclo[2.2.1]heptan-7-ylethyl)-4-[1S-methyl-2-(3-{pyridin-4-yl}piperidin-1-yl)carbonylamino-ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole</u>



F2 R10

4-Nitrophenyl chloroformate (183 mg ; 0.91 mmol) was added under an argon atmosphere, at 0°C, to a solution of **<u>F2</u>** (370 mg ; 0.82 mmol) and DIPEA (287 µl ; 1.65 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at 0°C for 30 minutes. 4-Piperidin-4-yl pyridine (186 mg ; 1.15 mmol) was added. The mixture was stirred for 16 hours and was purified by flash chromatography with increasingly polar solutions of EtOAc/CH_2Cl_2 (0-100% EtOAc) and then MeOH/CH_2Cl_2 (0-15% MeOH) to give **<u>R10</u>** as a pale yellow solid (190 mg).

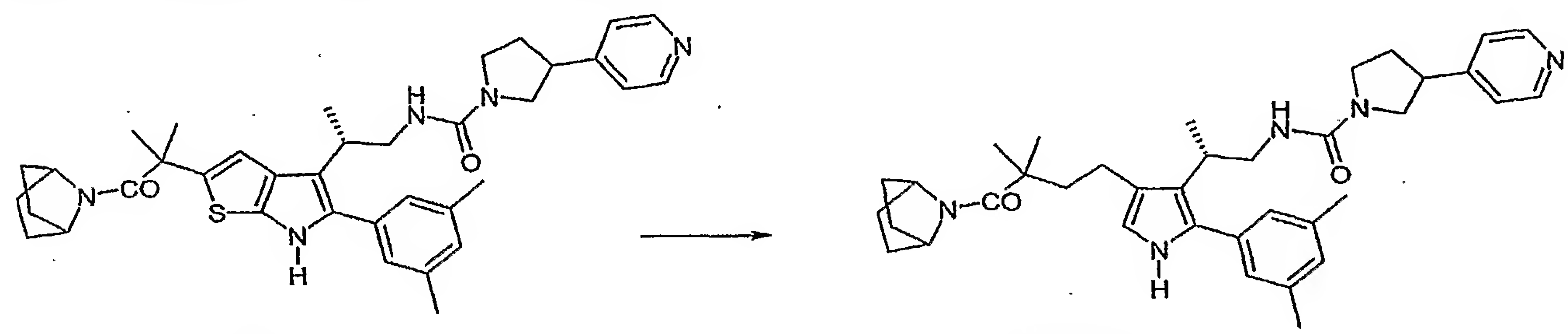
Yield : 36 %

^{1}H NMR spectrum ($CDCl_3$) : 1.32 (m, 4H) ; 1.36 (d, 3H) ; 1.63 (s, 6H) ; 1.6-1.8 (m, 8H) ; 2.33 (s, 6H) ; 2.58 (m, 1H) ; 2.70 (m, 2H) ; 3.24 (m, 1H) ; 3.32 (m, 1H) ; 3.75 (m, 2H) ; 3.96 (d, 1H) ; 4.12 (s br, 1H) ; 4.39 (m, 1H) ; 4.7 (s br, 1H) ; 6.79 (s, 1H) ; 6.94 (s, 1H) ; 7.04 (d, 2H) ; 7.07 (s, 2H) ; 8.26 (s, 1H) ; 8.49 (m, 2H).

MS-ESI : 638 $[M+H]^+$

Example 11

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-{3-(pyrid-4-yl)ppyrrolidin-1-ylcarbonylamino}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



R11 → Example 11

Example 11 was synthesised by the method used for preparing Example 1, except that a mixture of MeOH and EtOH was used as solvent. The following quantities of starting material and conditions were used: **R11** (367 mg ; 0.59 mmol) ; EtOH (5 ml) ; MeOH (5 ml); RaNi (10 g) ; hydrogen (1.5 atm.) ; 20 hours. **Example 11** was obtained as a white foam (31 mg).

Chromatography : MeOH/CH_2Cl_2 (0-10% MeOH)

Yield : 9%

^{1}H NMR spectrum ($CDCl_3$) : 1.29 (m, 9H) ; 1.46 (m, 4H) ; 1.78 (m, 4H) ; 1.91 (m, 3H) ; 2.3 (m, 1H) ; 2.31 (s, 6H) ; 2.53 (m, 2H) ; 3.15-3.45 (m, 5H) ; 3.65 (m, 2H) ; 4.20 (m, 1H) ; 4.66 (s br, 2H) ; 6.59 (d, 1H) ; 6.92 (s, 1H) ; 6.96 (s, 2H) ; 7.1 (m, 2H) ; 7.9 (s, 1H) ; 8.51 (s, 2H).

MS-ESI : 596 $[M+H]^+$

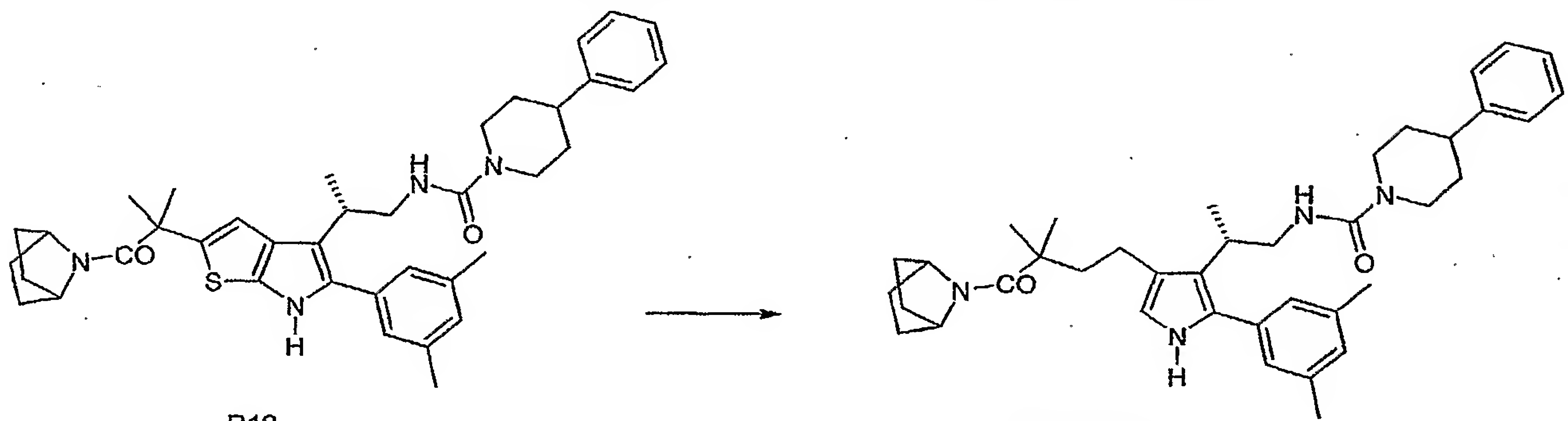
R11 was prepared using a method analogous to **R10** (see Example 10)

^{1}H NMR spectrum ($CDCl_3$) : 1.28 (m, 4H) ; 1.37 (d, 3H) ; 1.62 (s, 6H) ; 1.71 (m, 4H) ; 1.9 (m, 1H) ; 2.25 (m, 1H) ; 2.31 (s, 6H) ; 3.1-3.3 (m, 6H) ; 3.6 (m, 1H) ; 3.74 (m, 1H) ; 4.13 (s br, 1H) ; 4.14 (m, 1H) ; 4.7 (s br, 1H) ; 6.79 (s, 1H) ; 6.93 (m, 1H) ; 7.05 (m, 4H) ; 8.36 (s, 1H) ; 8.50 (m, 2H).

MS-ESI : 624 $[M+H]^+$

Example 12

3-[3,3-Dimethyl-4-oxo-4-(azabicyclo[2.2.1]heptan-7-yl)butyl]-4-[1S-methyl-2-{4-phenylpiperidin-1-ylcarbonylamino}ethyl]-5-(3,5-dimethylphenyl)-1H-pyrrole



Example 12 was synthesised by the method used for preparing Example 1, except that a mixture of MeOH and EtOH was used as solvent. The following quantities of starting material and conditions were used: **R12** (435 mg ; 0.68 mmol) ; EtOH (10 ml) ; MeOH (10 ml) ; RaNi (5 g) ; 16 hours. Example 12 was obtained as a yellow foam (258 mg).

Chromatography : EtOAc/hexanes (0-100% EtOAc)

Yield : 62%

^{1}H NMR spectrum ($CDCl_3$) : 1.29 (m, 9H) ; 1.46 (m, 4H) ; 1.75 (m, 8H) ; 1.91 (m, 2H) ; 2.31 (s, 6H) ; 2.55 (m, 3H) ; 2.71 (m, 2H) ; 3.21 (m, 2H) ; 3.63 (m, 1H) ; 3.80 (m,1H) ; 3.91 (m, 1H) ; 4.42 (d, 1H) ; 4.66 (s br, 2H) ; 6.59 (d, 1H) ; 6.92 (s, 1H) ; 6.98 (s, 2H) ; 7.12 (d, 2H) ; 7.20 (t, 1H) ; 7.28 (t, 2H) ; 7.88 (s, 1H).

MS-ESI : 609 $[M+H]^+$

R12 was prepared in the same manner as **R10** (see Example 10)

^{1}H NMR spectrum ($CDCl_3$) : 1.32 (m, 4H) ; 1.36 (d, 3H) ; 1.63 (s, 6H) ; 1.6-1.8 (m, 8H) ; 2.33 (s, 6H) ; 2.55 (m, 1H) ; 2.68 (m, 2H) ; 3.22 (m, 1H) ; 3.3 (m, 1H) ; 3.75 (m, 2H) ; 3.9 (d, 1H) ; 4.13 (s br, 1H) ; 4.38 (m, 1H) ; 4.7 (s br, 1H) ; 6.80 (s, 1H) ; 6.94 (m, 1H) ; 7.07 (s, 2H) ; 7.11 (d, 2H) ; 7.20 (t, 1H) ; 7.28 (m, 2H) ; 8.29 (s, 1H).

MS-ESI : 637 $[M+H]^+$

THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of

contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

i) anti-angiogenic agents (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);

ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

iii) biological response modifiers (for example interferon);

iv) antibodies (for example edrecolomab); and

v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4^{o}C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention

can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;

11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

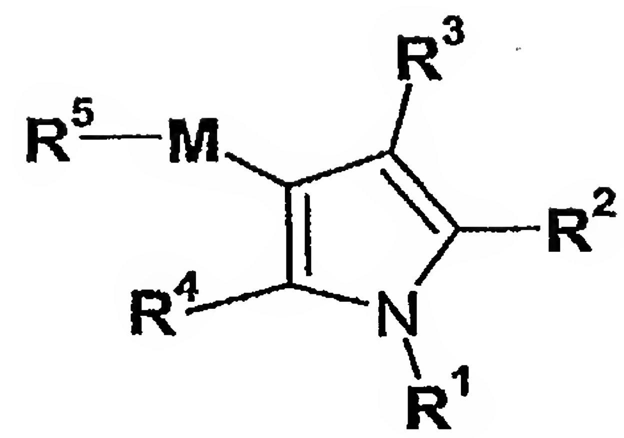
1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 µM.

CLAIMS:

1. A compound of Formula (I),



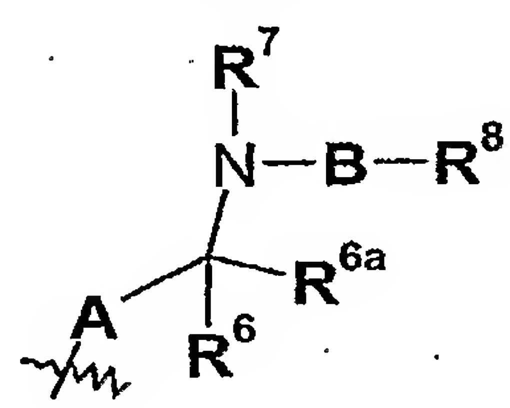
Formula (I)

wherein

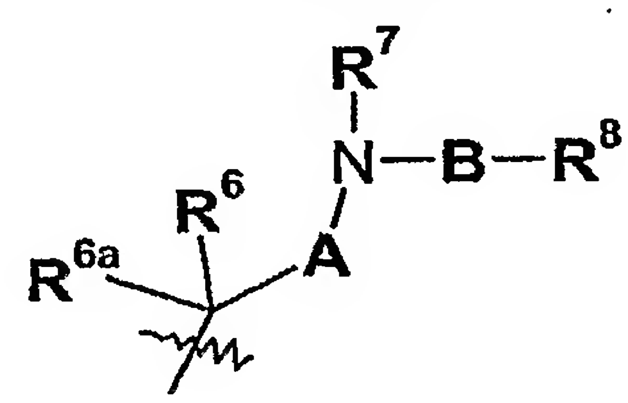
$\mathbf{R^1}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl or optionally substituted arylC_{1-6}alkyl, wherein the optional substituents are selected from C_{1-4}alkyl, nitro, cyano, fluoro and C_{1-4}alkoxy;

$\mathbf{R^2}$ is an optionally substituted mono or bi-cyclic aromatic ring, wherein the optional substituents are 1, 2 or 3 subsituents independently selected from: cyano, $\mathbf{R^e R^f}$N-, C_{1-6}alkyl, C_{1-6}alkoxy, halo, haloC_{1-6}alkyl or haloC_{1-6}alkoxy wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are independently selected from hydrogen, C_{1-6}alkyl or aryl;

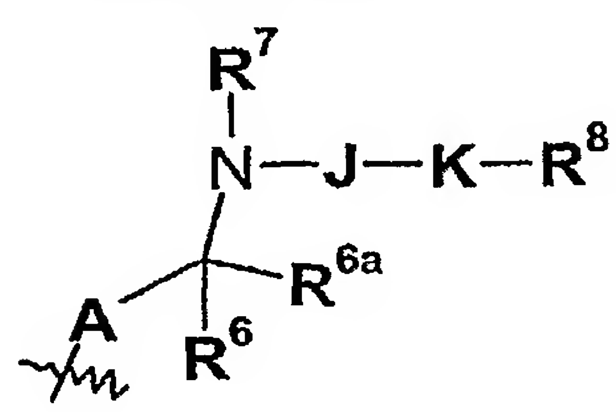
$\mathbf{R^3}$ is selected from a group of Formula (IIa) to Formula (IId):



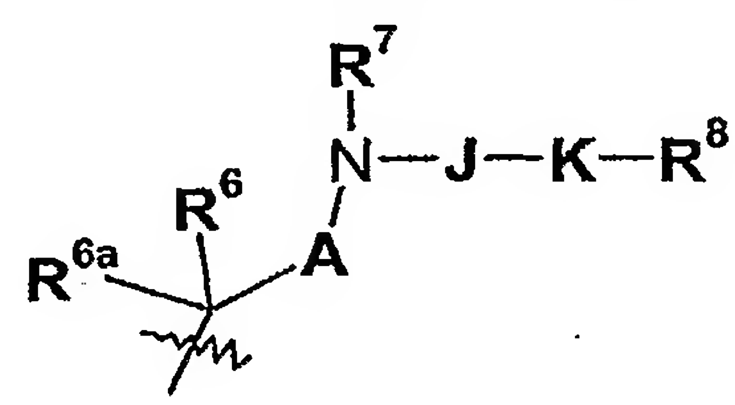
Formula (IIa)



Formula (IIb)



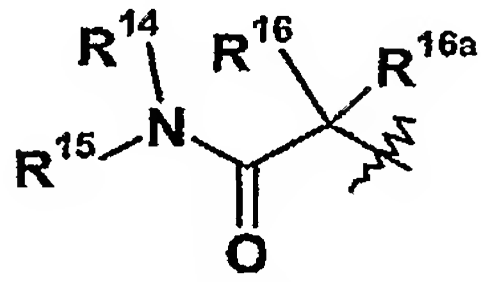
Formula (IIc)



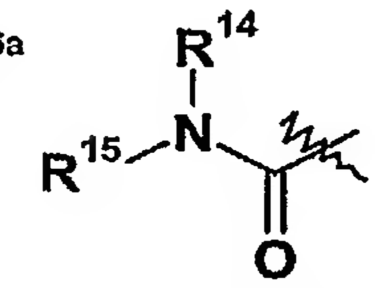
Formula (IId)

R^4 is selected from hydrogen, $C_{1\text{-}4}$alkyl or halo;

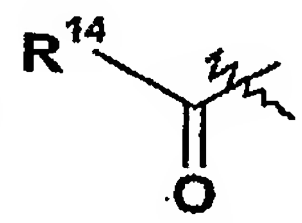
R^5 is selected from a group of Formula **III-a; III-b; III-c; III-d; III-e; III-f, III-g**, **III-h, III-i,** or **III-j, III-k, III-l, III-m, III-n** or **III-o**



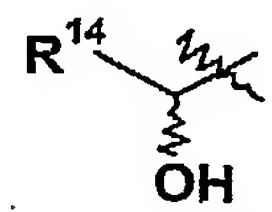
III-a



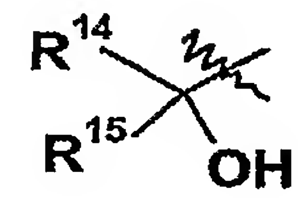
III-b



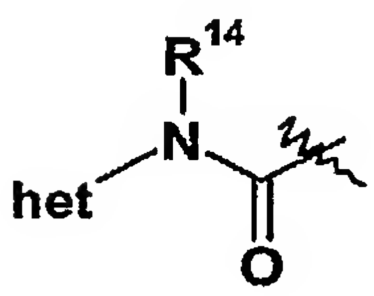
III-c



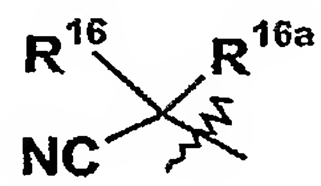
III-d



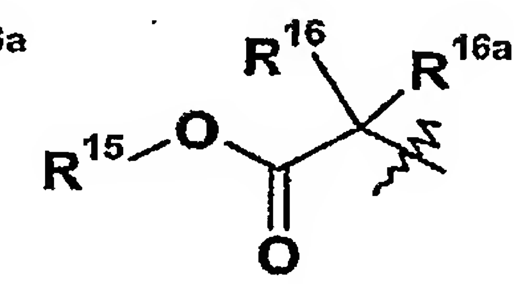
III-e



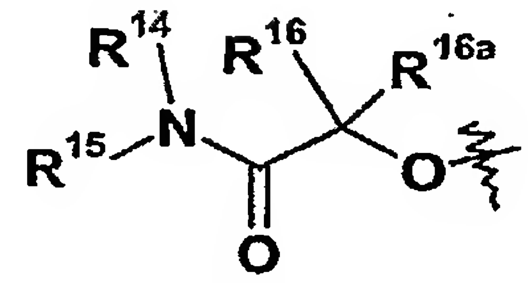
III-f



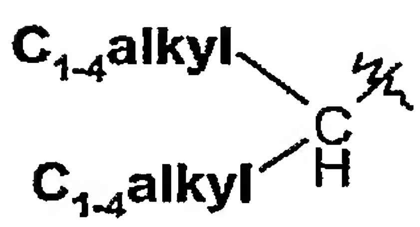
III-g



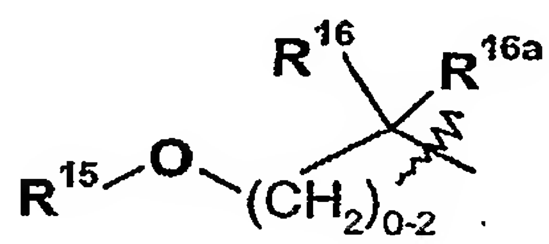
III-h



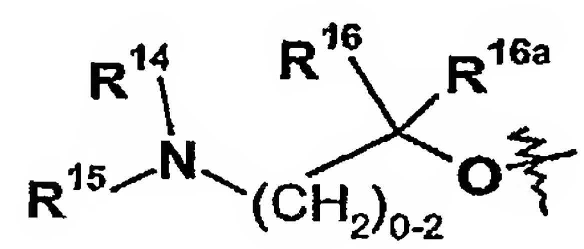
III-i



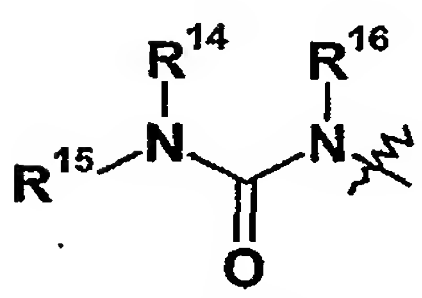
III-j



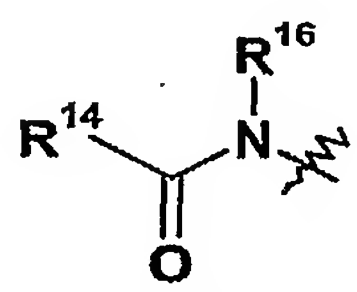
III-k



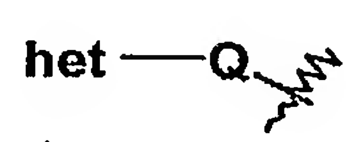
III-l



III-m



III-n



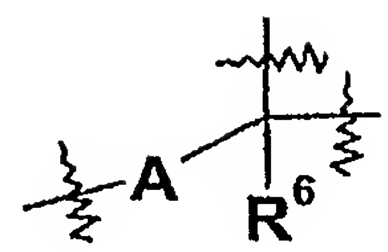
III-o

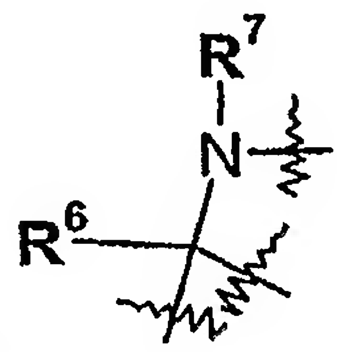
wherein:

het represents an optionally substituted 3- to 8-membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, wherein the optional substituents are selected from 1-2 groups selected from R^{12} and R^{13}; and

Q is selected from a direct bond or $-[C(R^{16}R^{16a})]_{1\text{-}2}-$

R^6 and R^{6a} are independently selected from hydrogen, fluoro, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

$\mathbf{R}^7$ is selected from: hydrogen or C_{1-6}alkyl;

$\mathbf{R}^8$ is selected from:

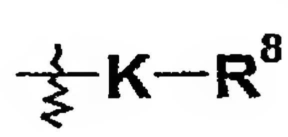
(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–S(O_n)-, -O-$\mathbf{R}^b$, –N$\mathbf{R}^b\mathbf{R}^c$, –C(O)-$\mathbf{R}^b$, –C(O)O-$\mathbf{R}^b$, -CON$\mathbf{R}^b\mathbf{R}^c$, NH-C(O)-$\mathbf{R}^b$ or –S(O_n)N$\mathbf{R}^b\mathbf{R}^c$,
where $\mathbf{R}^b$ and $\mathbf{R}^c$ are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by $\mathbf{R}^{12}$, or $\mathbf{R}^{13}$;

(iv) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by up to 4 substituents independently selected from $\mathbf{R}^{12}$ or $\mathbf{R}^{13}$;

$\mathbf{R}^9$ and $\mathbf{R}^{10}$ are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or $\mathbf{R}^9$ and $\mathbf{R}^{10}$ taken together can form an optionally substituted ring of 3-9 atoms, wherein the optional substituents are selected from $\mathbf{R}^{12}$ and


;

$\mathbf{R}^{11}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl or N($\mathbf{R}^9\mathbf{R}^{10}$);

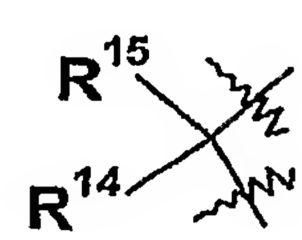
$\mathbf{R^{12}}$ is independently selected from: hydrogen, hydroxy, hydroxy$C_{1\text{-}6}$alkyl, oxo, cyano, cyano$C_{1\text{-}6}$alkyl, nitro, carboxyl, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkoxy$C_{0\text{-}2}$alkyl, $C_{1\text{-}6}$alkoxycarbonyl$C_{0\text{-}2}$alkyl, $C_{1\text{-}6}$alkanoyl$C_{0\text{-}2}$alkyl, $C_{1\text{-}6}$alkanoyloxy$C_{0\text{-}2}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{1\text{-}3}$perfluoroalkyl-, $C_{1\text{-}3}$perfluoroalkoxy, aryl, aryl$C_{1\text{-}6}$alkyl, heterocyclyl, heterocyclyl$C_{1\text{-}6}$alkyl, N-$C_{1\text{-}4}$alkylamino$C_{0\text{-}2}$alkyl, N, N-di-$C_{1\text{-}4}$alkylamino$C_{0\text{-}2}$alkyl, N-$C_{1\text{-}4}$alkylcarbamoyl$C_{0\text{-}2}$alkyl, N, N-di-$C_{1\text{-}4}$alkylaminocarbamoyl$C_{0\text{-}2}$alkyl, N-$C_{1\text{-}6}$alkyaminocarbonyl$C_{0\text{-}2}$alkyl, N, N-$C_{1\text{-}6}$alkyaminocarbonyl$C_{0\text{-}2}$alkyl, $C_{1\text{-}6}$alkyl-S(O)$_n$-amino$C_{0\text{-}2}$alkyl-, aryl-S(O)$_n$-amino$C_{0\text{-}2}$alkyl-, $C_{1\text{-}3}$perfluoroalkyl-S(O)$_n$-amino$C_{0\text{-}2}$alkyl-; $C_{1\text{-}6}$alkylamino-S(O)$_n$-$C_{0\text{-}2}$alkyl-, arylamino-S(O)$_n$-$C_{0\text{-}2}$alkyl-, $C_{1\text{-}3}$perfluoroalkylamino-S(O)$_n$-$C_{0\text{-}2}$alkyl-, $C_{1\text{-}6}$alkanoylamino-S(O)$_n$-$C_{0\text{-}2}$alkyl-; arylcarbonylamino-S(O)$_n$-$C_{0\text{-}2}$alkyl-, $C_{1\text{-}6}$alkyl-S(O)$_n$-$C_{0\text{-}2}$alkyl-, aryl-S(O)$_n$-$C_{0\text{-}2}$alkyl-, $C_{1\text{-}3}$perfluoroalkyl- or $C_{1\text{-}3}$perfluoroalkoxy$C_{0\text{-}2}$alkyl; wherein an amino group within $\mathbf{R^{12}}$ is optionally substituted by $C_{1\text{-}4}$alkyl;

$\mathbf{R^{13}}$ is $C_{1\text{-}4}$alkylaminocarbonyl optionally substituted by 1, 2 or 3 groups selected from $\mathbf{R^{12}}$;

$\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are selected from:

(i) $\mathbf{R^{14}}$ selected from hydrogen; optionally substituted $C_{1\text{-}8}$alkyl; optionally substituted aryl; -$\mathbf{R^d}$-Ar, where $\mathbf{R^d}$ represents $C_{1\text{-}8}$alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{15}}$ is selected from hydrogen; optionally substituted $C_{1\text{-}8}$alkyl and optionally substituted aryl;

(ii) wherein the group of Formula (III) represents a group of Formula **III-a , III-b, III-i, III-l** or **III-m**, then the group NR^{14}(-$\mathbf{R^{15}}$) represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) wherein the group of Formula (III) represents structure **III-e**, 

represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ are independently selected from:

(i) hydrogen or optionally substituted C_{1-8}alkyl; or

(ii) $\mathbf{R^{16}}$ and $\mathbf{R^{16a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

$\mathbf{R^{17}}$ is hydrogen or C_{1-4}alkyl;

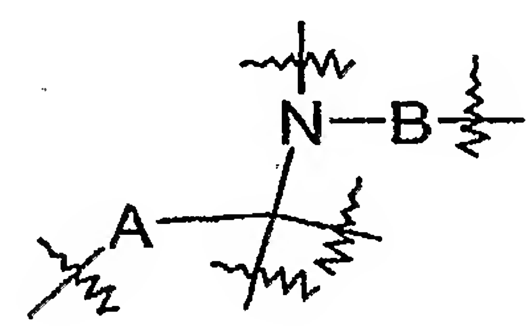
A is selected from:

(i) a direct bond;

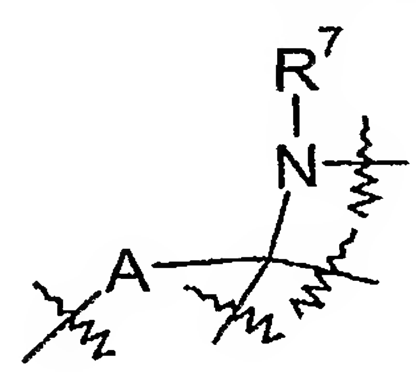
(ii) optionally substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, aryl or arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group or $-C(O)-C(\mathbf{R^d}\mathbf{R^d})$-, wherein $\mathbf{R^d}$ is independently selected from hydrogen and C_{1-2}alkyl;

or when $\mathbf{R^3}$ is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when $\mathbf{R^3}$ is a group of Formula (IIa), (IIb), (IIc) or (IId), the group

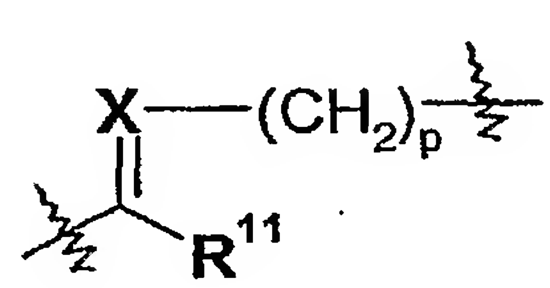


forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

wherein:

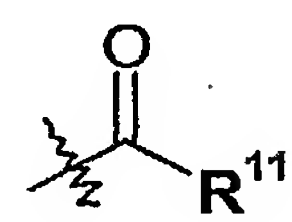
X is selected from N or CH,

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to $\mathbf{R^8}$; and

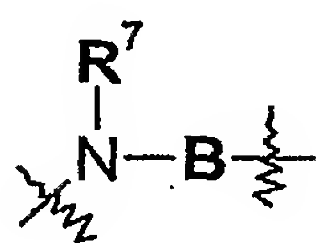
(iii) a group independently selected from: optionally substituted C_{1-6}alkylene, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}alkenylene, optionally substituted C_{3-6}alkynyl, $(C_{1-5}alkyl)_{aa}$-$S(O_n)$-$(C_{1-5}alkyl)_{bb}$-, -$(C_{1-5}alkyl)_{aa}$-O-$(C_{1-5}alkyl)_{bb}$-, -$(C_{1-5}alkyl)_{aa}$-C(O)-$(C_{1-5}alkyl)_{bb}$- or $(C_{1-5}alkyl)_{aa}$-N($\mathbf{R^{17}}$)- $(C_{1-5}alkyl)_{bb}$,

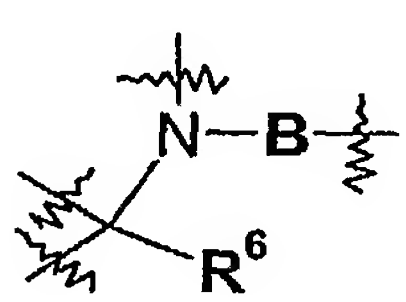
wherein $\mathbf{R^{17}}$ and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a heterocyclic ring, wherein the combined length of $(C_{1-5}alkyl)_{aa}$ and $(C_{1-5}alkyl)_{bb}$ is less than or equal to C_5alkyl and wherein the optional substituents are independently selected from $\mathbf{R^{12}}$;

or the group –**B**-$\mathbf{R^8}$ represents a group of Formula (V)

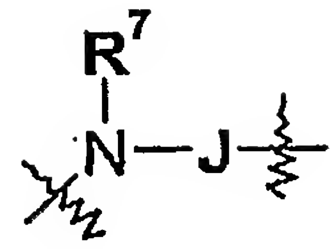


Formula (V);

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R^{12}}$ and $\mathbf{R^{13}}$;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

J is a group of the formula: -$(CH_2)_s$-**L**-$(CH_2)_s$- or -$(CH_2)_s$-C(O)-$(CH_2)_s$-**L**-$(CH_2)_s$-wherein when **s** is greater than 0, the alkylene group is optionally substituted,

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from 1 or 2 substituents independently selected from $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$;

K is selected from: a direct bond, $-(CH_2)_{s1}-$, $-(CH_2)_{s1}-O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-C(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-S(O_n)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R}^{17})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-C(O)N(\mathbf{R}^{17})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R}^{17})C(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R}^{17})C(O)N(\mathbf{R}^{17})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OC(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-C(O)O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R}^{17})C(O)O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OC(O)N(\mathbf{R}^{17})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OS(O_n)-(CH_2)_{s2}-$, or $-(CH_2)_{s1}-S(O_n)-O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-S(O)_2N(\mathbf{R}^{17})-(CH_2)_{s2}-$or $-(CH_2)_{s1}-N(\mathbf{R}^{17})S(O)_2-(CH_2)_{s2}-$; wherein the $-(CH_2)_{s1}-$ and $-(CH_2)_{s2}-$ groups are independently optionally substituted by hydroxy or C_{1-4}alkyl and wherein when s1>1 or s2>1 then the CH_2 group can optionally be a branched chain.;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

M is selected from $-CH_2-CH_2-$ or $-CH=CH-$;

n is an integer from 0 to 2;

p is an integer from 0 to 4;

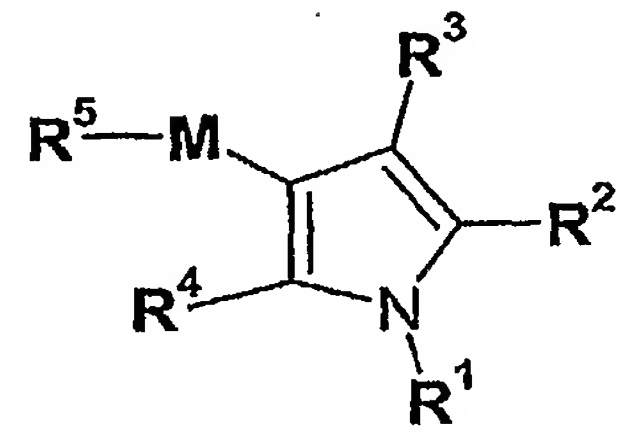
s, s1 and **s2** are independently selected from an integer from 0 to 4, and **s1+s2** is less than or equal to 4;

t is an integer between 0 and 4; and

or a salt, solvate or pro-drug thereof.

Abstract

The invention relates to a group of novel pyrazole compounds of Formula (I):



Formula (I)

wherein: R^1, R^2, R^3, R^4, M and R^5 are as defined in the specification, which are useful as gonadotrophin releasing hormone antagonists. The invention also relates to pharmaceutical formulations of said compounds, methods of treatment using said compounds and to processes for the preparation of said compounds.